I

Search results from the "OB_Rx" table for query on "020401."

Active Ingredient:	DILTIAZEM HYDROCHLORIDE
Dosage Form;Route:	CAPSULE, EXTENDED RELEASE; ORAL
Proprietary Name:	TIAZAC
Applicant:	BIOVAIL
Strength:	120MG
Application Number:	020401
Product Number:	001
Approval Date:	Sep 11, 1995
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	**AB4**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	DILTIAZEM HYDROCHLORIDE
Dosage Form;Route:	CAPSULE, EXTENDED RELEASE; ORAL
Proprietary Name:	TIAZAC
Applicant:	BIOVAIL
Strength:	180MG
Application Number:	020401
Product Number:	002
Approval Date:	Sep 11, 1995
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	**AB4**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	DILTIAZEM HYDROCHLORIDE
Dosage Form;Route:	CAPSULE, EXTENDED RELEASE; ORAL
Proprietary Name:	TIAZAC
Applicant:	BIOVAIL
Strength:	240MG
Application Number:	020401
Product Number:	003
Approval Date:	Sep 11, 1995
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	**AB4**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	DILTIAZEM HYDROCHLORIDE
Dosage Form;Route:	CAPSULE, EXTENDED RELEASE; ORAL
Proprietary Name:	TIAZAC
Applicant:	BIOVAIL
Strength:	300MG

Application Number:	020401
Product Number:	004
Approval Date:	Sep 11, 1995
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	**AB4**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	DILTIAZEM HYDROCHLORIDE
Dosage Form;Route:	CAPSULE, EXTENDED RELEASE; ORAL
Proprietary Name:	TIAZAC
Applicant:	BIOVAIL
Strength:	360MG
Application Number:	020401
Product Number:	005
Approval Date:	Sep 11, 1995
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	**AB4**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	DILTIAZEM HYDROCHLORIDE
Dosage Form;Route:	CAPSULE, EXTENDED RELEASE; ORAL
Proprietary Name:	TIAZAC
Applicant:	BIOVAIL
Strength:	420MG
Application Number:	020401
Product Number:	006
Approval Date:	Oct 16, 1998
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

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Patent Data Last Updated: February 18, 2005

Patent and Exclusivity Search Results from query on Appl No 020062 Product 004 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020062	004	4894240	JAN 16,2007			
020062	004	5002776	MAR 26,2008			
020062	004	5286497	MAY 20,2011			
020062	004	5364620	NOV 14,2011			U-3
020062	004	5439689	AUG 08,2012			U-107
020062	004	5470584	MAY 20,2011			

Exclusivity Data

There is no unexpired exclusivity for this product.

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Patent Data Last Updated: February 18, 2005

J

COMPARISON OF THE COMPOSITION OF VARIOUS DILTIAZEM COMPRISING PRODUCTS				
	CARDIZEM LA (T) SUBJECT INVENTION	CARDIZEM LA (C) SUBJECT INVENTION	TIAZAC (C) WO 93/00093	CARDIZEM CD (C) EP 0856313
	%w/w of coated active bead	%w/w of coated active bead	%w/w of coated active bead	%w/w of coated active bead
COMPONENT AND QUALITY STANDARD				
Core Active Bead Composition				
Diltiazem Hydrochloride, USP	70.15	70.45	73.03	42.35
Microcrystalline Cellulose, USP	8.77	8.81	9.1	-
Povidone K30, USP	1.30	1.32	1.4	-
Sucrose Stearate, House Std.	7.46	7.48	7.7	-
Fumaric Acid	-	-	-	10.59
Talc, USP	-	-	-	10.59
Silicon Dioxide, NF	-	-	-	0.32
Sugar Spheres	-	-	-	9.12
White Wax, NF	-	-	-	1.01
Ethylcellulose, NF	-	-	-	2.02
Castor oil, USP	-	-	-	0.67
Stearic Acid, NF	-	-	-	0.33
Isopropyl Alcohol, USP 99%	*	*	*	*
Coat Active Bead Composition				
Magnesium Stearate, NF	0.85	0.78	0.56	-
Talc, USP	0.85	0.78	0.56	-
Titanium Dioxide, USP	0.25	0.22	0.16	-
Hydroxypropyl Methylcellulose 2910, USP	0.48	0.45	0.32	-
Polysorbate 80, NF	0.02	0.02	0.013	-
Simethicone C Emulsion, USP	0.01	0.01	0.032	0.023
Eudragit NE30D, Ph.Eur.	9.85	9.18	6.6	-
Eudragit RS 30D solids	-	-	-	12.97
Eudragit RL 30D solids	-	-	-	0.66
Purified Water, USP	*	*	*	*
Talc†, USP	-	0.5	0.5	-
Amount of Coat Applied	~12%	~12%	~9%	~23%
Wax Placebo Beads (%w/w of tablet)				
Microcrystalline Wax, NF	20.29	-	-	-
Pregelatinized Starch, NF	13.59	-	-	-
Sodium Starch Glycolate, NF	6.69	-	-	-
Croscarmellose Sodium, NF	2.91	-	-	-
Colloidal Silicon Dioxide, NF	0.49	-	-	-
Hydrogenated Vegetable Oil, Type I, NF	4.85	-	-	-
Tablet Coating				
Opadry II White 49B18328, House Std.	2.94	-	-	-
Carnuba Wax, NF	0.01	-	-	-

* Evaporated during manufacturing process

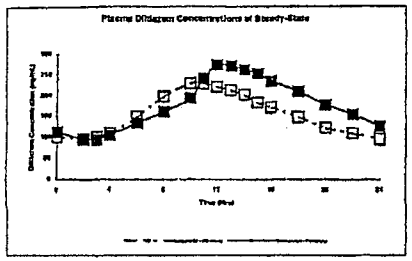
† Used as lubricant to prevent sticking of coated bead

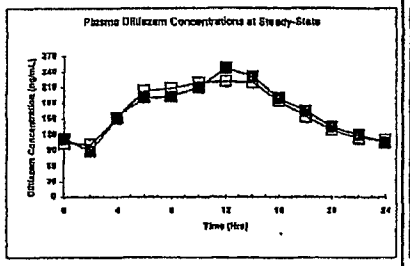
T=Tablet

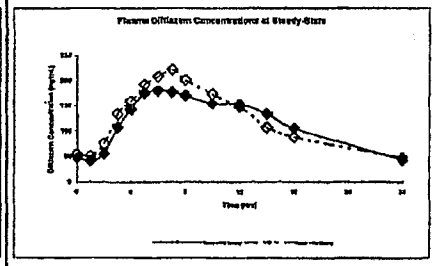
C=Capsule

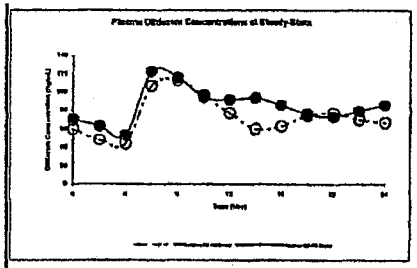
K

COMPARISON OF PHARMACOKINETIC PARAMETERS OF VARIOUS DILTIAZEM COMPRISING PRODUCTS









PARAMETERS	CARDIZEM LA 360 MG SUBJECT INVENTION		TIAZAC 360 MG WO 93/00093		CARDIZEM CD 240 MG EP 0856313	
	A.M. DOSING	P.M. DOSING	A.M. DOSING	P.M. DOSING	A.M. DOSING	P.M. DOSING
$AUC_{0-\tau}$	3691 ± 1449	4251 ± 1219	2870 ± 1005	2754 ± 810	2008 ± 814	1754 ± 715
C_{MAX}	274.5 ± 149.0	290.9 ± 94.0	243.2 ± 79.0	200.3 ± 59.1	137.7 ± 48.6	127.6 ± 47.8
PLASMA FLUCTUATION	118.9 ± 70.8	93.6 ± 29.5	171.4 ± 43.8	144.8 ± 26.7	112.5 ± 25.5	125.8 ± 31.2
	NIGHT/DAY RATIO		NIGHT/DAY RATIO		NIGHT/DAY RATIO	
$AUC_{0-\tau}$	1.15		0.96		0.87	
C_{MAX}	1.06		0.82		0.93	
PLASMA FLUCTUATION	0.79		0.85		1.12	

Note: Ratios of the pharmacokinetic parameters normalize for the different dosage strengths thereby allowing for a meaningful comparison of the pharmacokinetic parameters between the Cardizem LA, Tiazac and Cardizem CD.

1. CARDIZEM LA V TIAZAC

I. ANTICIPATION

'093 does not teach or inherently anticipate:

a. a composition having which provides a C_{max} of diltiazem in the blood at between about 10 – 15 hours,

b. a composition having a higher bioavailability at night (Cardizem LA Night/Day ratio = 1.15, Tiazac Night/Day ratio = 0.96),

c. a chronotherapeutic formulation of diltiazem (An orally administrable controlled-composition comprising a pharmaceutically acceptable form of diltiazem ... for evening dosing every 24 hours ... when said orally administrable composition ... results in a composition that ...(iii) provides a C_{max} of diltiazem in the blood at between about 10 hours and 15 hours after administration.)

II. OBVIOUSNESS

The composition of the Tiazac and Cardizem LA core is identical as is the composition of the coat. The ratio of the at least one hydrophilic polymer (HPMC) to the at least one water insoluble swellable neutral copolymer (Eudragit NE30D) is also identical (HPMC:NE30D = 20.5 for Cardizem LA, 20.6 for Tiazac). What is different is the amount of coat applied (~12% for Cardizem LA and ~9% for Tiazac). The Examiner may argue that it would have been obvious for the skilled artisan to increase the amount of coat in Tiazac from 9% to 12% to arrive at the subject invention. This would be incorrect for the following reasons:

a. There is no suggestion or motivation in '093 to increase the amount of coating to further delay the release of diltiazem. The aim of '093 is not to provide a chronotherapeutic formulation of diltiazem. '093 did not set out to solve the problem of reducing blood pressure during the critical morning hours of 6 a.m. to noon when the frequency of heart attacks and strokes is highest. The aim of '093 is to "provide galenic forms of Diltiazem with extended release of the active substance ... having excellent bioavailability while avoiding plasmatic concentration peaks." Page 2, lines 28-33. Accordingly, '093 does not provide any motivation to alter the release rate of diltiazem to provide for a chronotherapeutic formulation.

b. This seemingly trivial increase in the amount of coat applied results in a significant clinical advantage. There is no motivation or suggestion that the formulation taught in '093 will provide for a higher bioavailability when administered during the evening hours. In fact, nowhere in '093 does it disclose when during the day its own formulation of Example 4 was administered, nor is there any suggestion or motivation that increasing the amount of coat applied will lead to a formulation which will provide a higher bioavailability when administered at night and have an even lower plasma fluctuation than the formulation taught in '093. While it is well known in the art that increasing the amount of a coat applied may lead to a delay in the release of a drug, there is no reason *a priori* to assume from general knowledge, and certainly not from the teachings of '093, that increasing the amount of coat applied would also result in other benefits, namely higher bioavailability when administered at night and lower plasma fluctuation. This is in and of itself is a surprising result.

c. Even though the in-vitro release rates of the two compositions overlap, the '093 formulation inherently does not, and cannot, provide for a chronotherapeutic composition. This is unequivocally demonstrated by the comparative pharmacokinetic data presented above.

d. The examiner could argue that '093 could come up with a formulation whose in-vitro dissolution rate fell within the overlapping ranges and that such a formulation would inherently lead to a chronotherapeutic formulation of the presently claimed invention. Not so. For '093 to provide a chronotherapeutic profile, its in-vitro dissolution profile must fit within the presently claimed in-vitro range over the entire 24 hr testing period. '093 provides in-vitro dissolution rates only up to 8 hrs.

What happens to the dissolution rate after that? To extrapolate beyond 8 hrs for '093 would be incorrect, but given a 9% coat, it is reasonable to assume that that the rate of release will be much faster and that more than 75% release would be achieved before 24 hrs and perhaps even before 14 hrs.

e. The '093 formulation provides a C_{max} of diltiazem at between 7 – 8 hours (see Figures 1 and 2 in '093). Even if the '093 formulation is administered during the evening hours of between 8 – 10 pm the diltiazem levels would peak between the hours of 3 – 6 am. This would be too early for Tiazac to have any therapeutic significance.

f. For the examiner to say that it would have been obvious for the skilled artisan to increase the amount of coat applied from 9% to 12% to arrive at the present invention would be use hindsight, which is not permissible. Even if '093 taught or suggested a chronotherapeutic formulation, which it does not, there is no teaching of how much of the coat should be applied to arrive at the presently claimed invention. Will 9.5, 10, 11, 12, 13, 14, 15% or more of the coat be sufficient to obtain a chronotherapeutic formulation? An undue amount of experimentation would be required to determine the optimal amount of coat to be applied to arrive at a chronotherapeutic formulation. The in-vtro dissolution properties for a particular drug do not necessarily or predictability correlate with a desired in-vivo pharmacokinetic profile. The design of a formulation which achieves a desired combination of both in-vitro and in-vivo profiles requires trial and error experimentation i.e., undue experimentation.

2. CARDIZEM LA v CARDIZEM CD

I. ANTICIPATION

'313 does not teach or inherently anticipate:

a. a composition having a neutral copolymer. Claim 10 of '313 teaches the use of a copolymer of acrylic and methacrylic acid ester. However, the term "copolymer of acrylic and methacrylic acid ester" construed in light of the disclosure only teaches charged copolymers.

b. A composition having a higher bioavailability at night (Cardizem LA Night /Day ratio = 1.15, Cardizem CD Night/Day ratio = 0.87).

II. OBVIOUSNESS

a. The teaching in '313 is limited to charged copolymers. Accordingly, the skilled artisan would not deviate from this teaching to use a neutral copolymer. To do so would require undue experimentation, thus making the presently claimed invention unobvious.

b. There is no suggestion or motivation that using a neutral copolymer might result in a formulation having a higher bioavailability and lower plasma fluctuation when administered in the evening. We, however, would submit that in this case, the use of the neutral copolymer isn't the only differentiating factor over '313. It is the use of a neutral copolymer as well as the amount of coating applied to provide for a specific in-vitro and in-vivo release profile. This complexity would not be readily apparent to the skilled artisan from reading '313.

2. OTHER COMMENTS

a. The one thing that did come out of our interview with the Examiner was that in his view we were trying to claim the world of neutral copolymers. Not so. The neutral copolymer claimed is limited to one that is a water insoluble swellable neutral copolymer. Table II of Exhibit 12 (column labeled "solubility") shows only one copolymer with such a characteristic, namely Eudragit NE30D (see also Section 8 under the heading "Eudragit NE30D"). Limiting the claim to "Eudragit NE30D" would, however, be unduly limiting. Eudragit NE30D belongs to the acrylic family of copolymers. There is another neutral copolymer, which belongs to polyvinylic family – Kollicoat SR 30 D. Kollicoat SR 30 D is a neutral copolymer (see page 6 of the Kollicoat SR 30 D Spec Sheet attached), which is insoluble in dilute alkaline and acidic solutions (see page 3 of Spec Sheet). *Note: The "Kollicoat 30 D" referred to in Table II of Exhibit 12 is NOT "Kollicoat SR 30D". The Kollicoat referred to therein is" Kollicoat MAE 30D".* Kollicoat SR 30 D is also a swellable polymer (see picture on top of page 2 of BASF article). We are not sure when Kollicoat SR 30 D was first commercialized, but we think it was after our earliest filing date and accordingly Kollicoat SR 30D would be an unforeseen equivalent. I am tracking down the date Kollicoat SR 30 D was first commercialized.

L

AJH 2003; 16:51-58

Efficacy and Safety of a Once Daily Graded-Release Diltiazem Formulation in Essential Hypertension

Stephen P. Glasser, Joel M. Neutel, Theophilus J. Gana, and Kenneth S. Albert

Background: The efficacy and safety of a chronotherapeutic, graded-release diltiazem HCl extended-release (GRD) 120-, 240-, 360- and 540-mg dose administered once-daily at bedtime (10 PM) were evaluated in a 7-week randomized, double-blind comparison to placebo and to GRD 360 mg administered once-daily at 8 AM in 478 patients with moderate-to-severe essential hypertension.

Methods: We assessed the change from baseline to end point in trough diastolic blood pressure (DBP) at 6 PM to 10 PM and in mean DBP from 6 AM to 12 noon between GRD 360 mg PM and GRD 360 mg AM, measured by ambulatory BP monitoring (ABPM).

Results: Bedtime doses of GRD showed dose-related mean reductions in trough DBP that were significant for GRD doses of 240 mg and higher. Bedtime GRD 360 mg was associated with a significantly greater reduction in mean DBP between 6 AM and 12 noon compared to morning GRD 360 mg with a least squares mean for treatment difference of −3.3 mm Hg (P = .0004). Similar dose-related and significant reductions in systolic BP (SBP) and heart rate (HR) were obtained. Incidence of adverse events (AEs) for all GRD groups (44.5%) was less than that obtained for the placebo group (49.3%). The 540-mg group showed an incidence of AEs (43.5%) similar to that observed for the 240-mg group (42.6%).

Conclusions: The GRD dose-dependently significantly reduces BP and HR over the 24-h interval after once-daily bedtime dosing. Further greater reductions were obtained between 6 AM and 12 noon, when circadian BP is highest, compared to morning administration of the same dose. The 540-mg GRD was safe, well tolerated, and offers further therapeutic option for patients with severe hypertension who required additional BP control. Am J Hypertens 2003;16:51–58 © 2003 American Journal of Hypertension, Ltd.

Key Words: Diltiazem extended release, hypertension, chronotherapy, nighttime dosing.

Results of several large epidemiologic studies have shown that there is an increased incidence of nonembolic stroke,[1,2] silent myocardial ischemia,[3,4] myocardial infarction,[1,5,6] and sudden cardiac death[1,7,8] in the early morning period, between 6 AM and 12 noon. This peak incidence of cardiovascular events coincides with the period of the early morning surge in blood pressure (BP) and heart rate (HR) in normotensive and hypertensive individuals.[9,10] Although several potential triggers for cardiovascular events have been identified during the early morning period, there is growing evidence of an important association between the early morning surge in BP and myocardial ischemia. Consequently, this has led to the need to develop chronotherapeutic antihypertensive medications, which synchronize their antihypertensive effect with the body's circadian rhythm of BP, thereby optimizing control.

Recently, a new once-daily, graded-release formulation of diltiazem (GRD), designed to achieve maximum plasma levels between the critical morning hours of 6 AM and 12 noon when dosed at night has been developed. Pharmacokinetic studies comparing nighttime administration of GRD to morning administration of an identical dose showed peak plasma concentrations during the period 6 AM to 12 noon.[11] Because plasma concentrations of diltiazem are known to correlate with its antihypertensive effects,[12–14] the latter results suggest that GRD may be an ideal chronotherapeutic agent for the management of hypertension. To date, no chronotherapeutic diltiazem formulation has been approved for mar-

Received July 1, 2002. First decision July 25, 2002. Accepted September 5, 2002.

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0895-7061/03/$30.00
PII S0895-7061(02)03153-9

keting in the United States by the Food and Drug Administration.

In this study, we have assessed four doses of GRD, 120-mg PM, 240-mg PM, 360-mg PM and AM, and 540-mg PM compared to placebo in stages II and III hypertension.[15] A unique feature of this study was a comparison of the safety and efficacy of 360-mg dosed PM and AM, and a 540-mg dose of diltiazem.

Methods

Study Design

A total of 59 centers in the United States participated in this randomized, double-blind, parallel-group, dose-response, placebo-controlled, multicenter study. The study protocol and amendments were approved by an appropriately constituted central or local Institutional Review Board. The study consisted of an initial screening period followed by a 3- to 4-week single-blind, placebo run-in period. Thereafter, patients were randomized to receive either placebo or active treatment (GRD—Biovail Laboratories, Steinbach, Manitoba, Canada), for a 7-week double-blind treatment period as follows: placebo, GRD 120-mg PM, GRD 240-mg PM, GRD 360-mg AM, GRD 360-mg PM, or GRD 540-mg PM in a ratio of 1:1:1:1.5:1.5:1 by telephone from an Interactive Voice Response System (IVRS). Patients randomized to 540 mg had an initial 1-week titration period on 360 mg, followed by forced titration to 540 mg from weeks 2 to 7. Patients randomized to the remaining groups received their respective doses throughout the 7-week treatment period.

Study medications were taken each morning at 8 AM ± 1 h (360-mg AM only) and evening at 10 PM ± 1 h. Patients were evaluated for safety and efficacy at weekly intervals during the run-in and titration periods, and at 2-week intervals during the double-blind treatment period.

Patients

Adult male and female patients, aged 18 to 70 years, with moderate-to-severe essential hypertension who gave written informed consent were included into the study if their average seated systolic blood pressure (SBP) was <200 mm Hg and mean seated diastolic blood pressure (DBP) was ≥100 mm Hg and ≤114 mm Hg at rest on 2 consecutive weeks during the run-in period. Furthermore, the average seated DBP readings at the two qualifying visits could not vary by more than 7 mm Hg. In addition, patients were eligible for randomization only if their mean daytime (8 AM to 4 PM) DBP by ambulatory BP monitoring (ABPM) was ≥90 mm Hg and ≤114 mm Hg at baseline.

Patients were excluded from the study if they had a recent history of serious cardiovascular or cerebrovascular events, secondary hypertension, or any serious chronic or uncontrolled medical conditions. In addition, nightshift workers and patients with a known sensitivity to diltiazem were excluded.

Measurements of BP and HR

A 36-h ABPM was performed on each patient at baseline and at the end of the double-blind treatment period using a Spacelabs 90207 monitor (Spacelabs, Inc., Redmond, WA). The ABPM monitor was applied to the patient's nondominant arm at 6 PM ±1 h, and the patients were instructed to dose this medication at 10 PM ± 1 h that night, and to return to the clinic the next morning at 8 AM ±1 h to have the monitor checked. The next morning trough office cuff seated BP measurements were obtained at 8 AM ±1 h. The ABPM was programmed to take one measurement every 20 min during the 24-h interval. The patient returned to the clinic again the following morning (after 36 h of ABPM application) at 8 AM ±1 h to have the monitor removed and the recorded data downloaded.

In addition, seated office BP measurements were taken at all clinic visits. The average of three BP measurements taken 2 min apart after the patient had been sitting quietly for 5 min was used. Seated HR was measured after the second BP determination. Office cuff BP measurements were obtained at 6 PM ±1 h (trough for PM dosing) and at 8 AM ±1 h (trough for AM dosing) on the days ABPM was performed.

Efficacy Parameters

One primary measure of efficacy was the change from baseline to end point in trough DBP, recorded between 6 PM and 10 PM by ABPM, for the evening GRD treatment groups (GRD 120 mg, 240 mg, 360 mg PM and 540 mg) compared with placebo. The co-primary was the change from baseline to end point in mean DBP recorded by ABPM between 6 AM and 12 noon for GRD 360 mg AM compared to 360 mg PM.

Twelve secondary efficacy variables assessed the changes from baseline to end point in SBP, DBP, and HR by ABPM and clinic measurements, for the periods 4 AM to 8 AM, 6 AM to 12 noon, 6 PM to 10 PM, and the overall 24-h mean.

Responder rates were also determined for BP values assessed by office cuff sphygmomanometry. The DBP responder rate was defined as the proportion of patients achieving a mean DBP <90 mm Hg at end point or a decrease of at least 10 mm Hg from the baseline mean DBP; SBP responder rate was defined as the proportion of patients achieving a mean SBP <140 mm Hg at end point or a decrease of at least 10% from the baseline mean SBP.

Statistical Analysis

All statistical analyses were performed using SAS Version 6.12 or higher (Statistical Analysis System Institute, Inc., Cary, NC). Intent-to-treat analyses of efficacy data were performed. Separate analysis of covariance (ANCOVA) models were used to analyze each continuous primary and secondary efficacy variable, using the change from baseline to end point as the dependent variable, treatment and study site as the main effects, and baseline BP included as

a covariate. The treatment-by-baseline and treatment-by-site interactions were examined. Multiple comparisons between the placebo group and each active treatment group were made using Dunnett's test. Responder rates were summarized by counts and percentages, and compared between treatment groups using Fisher's exact test.

Sample size was determined based on the change from baseline to end point in the mean DBP between 6 AM and 12 noon as measured by ABPM between the GRD 360-mg PM and 360-mg AM treatment groups. Assuming a common standard deviation of 8 mm Hg, it was estimated that 99 patients in each 360-mg group (AM and PM) and 66 in each of the other groups will provide greater than 80% power to detect a mean difference of 4 mm Hg between the two 360-mg groups, and a mean difference of 5 mm Hg between the rest of the groups at the 0.05 level of significance. Hence, 462 patients were planned for randomization.

Results

Patient Disposition

A total of 478 patients were randomized and received at least one dose of study medication; overall, 429 (89.1%) of these patients completed the study. The patient demographics and baseline characteristics are summarized in Table 1. The most common reason for premature withdrawal from the double-blind period was an adverse event, in 3.2% of GRD-treated patients and 4.3% of placebo-treated patients. Other reasons for withdrawal included noncompliance, withdrawal of consent, and lack of efficacy.

Efficacy Results

Blood Pressure The mean ± SD reductions in trough SBP, DBP, and HR measured by ABPM between 6 PM and 10 PM in all treatment groups are summarized in Table 2. The mean reductions in trough DBP were dose related and were statistically significant for the GRD 240-mg ($P < .0001$), 360-mg ($P = .002$), and 540-mg ($P < .0001$) groups. The largest mean reduction in trough DBP was observed in the 540-mg group. Similarly, there were dose-related, mean reductions in trough (6 PM to 10 PM) SBP from baseline to end point for all evening GRD groups (Table 2), which were only statistically significant for the GRD doses greater than 120 mg. The 540-mg group also showed the greatest reduction. The greater reductions in BP observed for the 240-mg dose (DBP: −5.3 mm Hg; SBP: −8.1 mm Hg) compared with the 360-mg PM dose (DBP: −3.3 mm Hg; SBP: −4.6 mm Hg), may be due to significant baseline BP differences between the two groups. There was a 5 mm Hg difference in DBP and a 7.5 mm Hg difference in SBP between the two groups (Table 1). This is especially likely because with diltiazem, the extent of the BP reduction is related to the severity of the baseline hypertension.[12,16,17] The least squares mean results, adjusting for baseline differences, confirmed the dose-related reductions in trough DBP and eliminated the latter difference in the responses observed between the GRD 240-mg and 360-mg PM treatment groups. The least squares means for the change from baseline to end point in trough DBP were: −1.92 mm Hg, −4.26 mm Hg, −4.38 mm Hg, and −8.02 mm Hg, respectively, for GRD 120-, 240-, 360-mg PM and 540-mg treatment groups (Fig. 1A). Similar least squares mean results were obtained for the corresponding change from baseline to end point in trough SBP (Fig. 1A).

There was a significant difference between the GRD 360-mg PM and 360-mg AM groups in the mean change from baseline to end point in DBP measured by ABPM between 6 AM and 12 noon (Table 2). The least squares mean for treatment difference was −3.30 mm Hg ($P = .0004$) for DBP (Fig. 1B). For SBP, similar results were obtained (Table 2) with a least squares mean for treatment difference of −5.32 mm Hg ($P = .0004$) in favor of the PM treatment group (Fig. 1B). In addition, there was a significant ($P < .0001$), dose-related increase in the antihypertensive effect observed between 6 AM and 12 noon for all the GRD evening doses with the 540-mg group showing the greatest effect (Fig. 1B).

The 24-h DBP (Fig. 2A) and SBP (Fig. 2B) profiles for the GRD 360-mg PM, 360-mg AM, and placebo treatment groups obtained by ABPM after 7 weeks of treatment, using the mean hourly values, showed bedtime administration of GRD provided the greatest antihypertensive effect, for DBP and particularly SBP, during the critical morning period (about 6 AM to 12 noon) and the least effect during the hours of 2 to 4 AM, when BP is at its lowest. The lower reductions in the 24-h mean DBP and SBP for the GRD 360-mg AM group compared to the 360-mg PM group (Table 2) can similarly be attributed to the lower baseline BP values of the PM group, as shown previously in other reports.[18,19]

The DBP responder rates achieved for all GRD treatment groups above the 120-mg dose were significantly ($P < .05$) higher than those observed for placebo (Fig. 3). For SBP, only the GRD 240-mg and 540-mg treatment groups achieved significantly higher responder rates compared to placebo. The SBP responder rates for the 360-mg groups did not achieve statistical significance, probably because the significantly lower baseline BP values (Table 1) reduced the extent of the antihypertensive response.[16,17,19] Overall, the largest responder rates were observed in the 540-mg treatment group and were 73.4% for DBP and 67.2% for SBP. Between the 360-mg PM and 360-mg AM groups, the responder rates were similar.

Heart Rate There were dose-related mean reductions in HR from baseline to end point during the time periods assessed (Table 2), with the greatest reductions seen during the 6 AM to 12 noon period. The mean reductions in 24-h HR were only significant ($P < .05$) for the GRD doses above 240 mg. Compared to placebo, only the mean 24-h reductions for the GRD 360-mg doses and higher

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Table 1. Patient demographics and baseline characteristics

Characteristic	Placebo (n = 69)	GRD 120 mg (n = 67)	GRD 240 mg (n = 68)	GRD 360 mg AM (n = 102)	GRD 360 mg PM (n = 103)	GRD 540 mg (n = 69)	*P*
Age (y)	51.5 ± 9.6	51.6 ± 10.3	52.8 ± 9.2	53.6 ± 9.6	52.5 ± 8.4	51.4 ± 9.5	.6103
Height (cm)	171.2 ± 10.8	170.5 ± 9.6	173.6 ± 9.5	171.9 ± 9.7	172.8 ± 10.2	172.0 ± 8.3	.4792
Weight (kg)	92.5 ± 18.3	86.6 ± 17.4	90.5 ± 19.7	94.5 ± 22.9	91.8 ± 18.0	92.1 ± 18.0	.3501
Gender - n (%)							.7023
Male	45 (65.2)	46 (68.7)	42 (61.8)	61 (59.8)	69 (67.0)	40 (58.0)	
Female	24 (34.8)	21 (31.3)	26 (38.2)	41 (40.2)	34 (33.0)	29 (42.0)	
Ethnicity - n (%)							.2151
White	45 (65.2)	35 (52.2)	42 (61.8)	66 (64.7)	67 (65.0)	47 (68.1)	
African American	16 (23.2)	22 (32.8)	24 (35.3)	28 (27.5)	28 (27.2)	14 (20.3)	
Other	8 (11.5)	10 (15.0)	2 (3.0)	8 (7.8)	8 (7.8)	8 (11.5)	
Baseline ABPM parameters	(n = 59)	(n = 61)	(n = 64)	(n = 95)	(n = 96)	(n = 64)	
Trough (6 PM–10 PM)*							
SBP (mm Hg)	155.7 ± 14.1	154.9 ± 14.4	160.7 ± 14.7	151.5 ± 19.9	153.2 ± 14.5	156.4 ± 15.8	.0061
DBP (mm Hg)	98.6 ± 8.3	97.8 ± 9.6	100.3 ± 9.5	92.5 ± 10.6	95.3 ± 9.8	98.3 ± 10.1	.0398
HR (beats/min)	85.0 ± 12.6	81.3 ± 13.2	84.7 ± 10.1	75.7 ± 10.1	83.8 ± 11.8	85.3 ± 13.1	.4718
6 AM–12 noon							
SBP (mm Hg)	156.6 ± 12.7	155.2 ± 12.5	159.3 ± 13.7	161.0 ± 17.1	156.0 ± 12.2	157.3 ± 12.7	.0718
DBP (mm Hg)	101.7 ± 7.4	100.1 ± 7.1	101.7 ± 8.3	100.3 ± 8.1	100.1 ± 7.0	100.7 ± 6.7	.6190
HR (beats/min)	80.6 ± 10.3	79.1 ± 10.8	80.4 ± 10.1	82.9 ± 9.6	82.0 ± 11.4	82.1 ± 10.0	.2609
24-h mean							
SBP (mm Hg)	151.2 ± 12.3	150.4 ± 11.8	154.5 ± 12.6	156.0 ± 16.6	150.5 ± 12.0	151.6 ± 12.7	.0300
DBP (mm Hg)	96.0 ± 7.0	95.0 ± 6.5	96.5 ± 7.4	94.9 ± 7.4	94.3 ± 6.4	95.2 ± 6.9	.4141
HR (beats/min)	80.2 ± 9.9	78.2 ± 10.8	80.1 ± 8.6	81.5 ± 8.9	80.7 ± 10.2	80.8 ± 9.8	.4672

GRD = graded-release diltiazem HCl extended release; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.
Values are mean ± SD.
* Trough values for GRD 360 mg AM are for the period 4 AM to 8 AM.

Table 2. Change from baseline to end point in mean DBP, SBP, and HR recorded by ABPM

Period	Placebo (n = 57)	GRD 120 mg (n = 59)	GRD 240 mg (n = 63)	GRD 360 mg AM (n = 94)	GRD 360 mg PM (n = 95)	GRD 540 mg (n = 62)
Trough (6 PM–10 PM)*						
SBP (mm Hg)	0.5 ± 12.2	−2.8 ± 13.0	−8.1 ± 12.7†‡	−8.4 ± 10.7†‡	−4.6 ± 12.9†‡	−9.9 ± 13.2†‡
DBP (mm Hg)	−0.2 ± 7.8	−2.1 ± 9.2‡	−5.3 ± 9.6†‡	−6.4 ± 7.7†‡	−3.3 ± 10.0†‡	−8.2 ± 9.1†‡
HR (beats/min)	−1.5 ± 10.5	−0.2 ± 10.1	−1.5 ± 8.8	−4.2 ± 6.8†	−4.6 ± 9.3†	−5.4 ± 9.1†
6 AM–12 noon						
SBP (mm Hg)	0.5 ± 11.5	−5.9 ± 10.8†‡	−12.6 ± 11.3†‡	−8.4 ± 9.8†‡	−12.0 ± 9.5†‡	−18.5 ± 12.5†‡
DBP (mm Hg)	−0.3 ± 8.0	−4.5 ± 6.9†‡	−9.3 ± 7.7†‡	−6.8 ± 5.9†‡	−9.9 ± 7.0†‡	−14.8 ± 8.2†‡
HR (beats/min)	0.5 ± 8.7	−0.7 ± 7.4	−3.2 ± 7.7†‡	−5.1 ± 7.9†‡	−5.8 ± 9.7†‡	−8.3 ± 8.7†‡
24-h mean						
SBP (mm Hg)	1.0 ± 7.7	−4.3 ± 9.0†‡	−9.2 ± 8.8†‡	−10.1 ± 8.3†‡	−8.2 ± 7.7†‡	−13.5 ± 9.7†‡
DBP (mm Hg)	−0.1 ± 5.0	−2.9 ± 5.3†‡	−5.9 ± 5.8†‡	−8.1 ± 5.1†‡	−6.6 ± 5.2†‡	−10.8 ± 6.1†‡
HR (beats/min)	−0.3 ± 6.9	−0.4 ± 5.2	−2.4 ± 6.1†	−6.1 ± 6.4†‡	−4.6 ± 6.9†‡	−6.7 ± 6.2†‡

Abbreviations as in Table 1.
Values are mean ± SD.
* Trough values for GRD 360 mg AM are for the period 4 AM to 8 AM; †$P < .05$ for change from baseline to end point; ‡$P < .05$ v placebo.

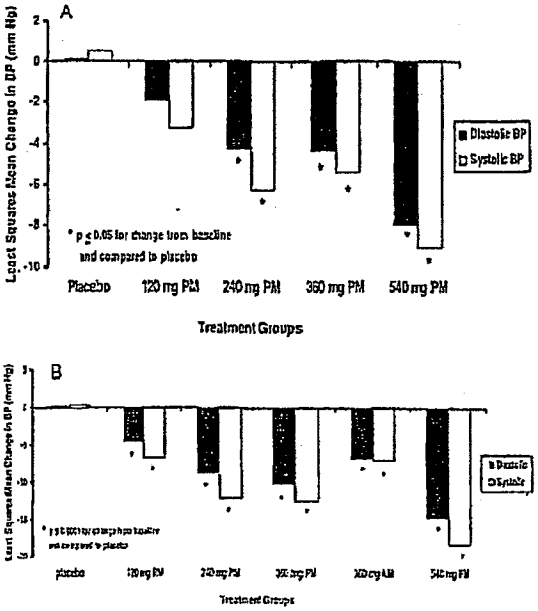

FIG. 1. A) Least squares mean changes from baseline in trough diastolic and systolic blood pressure (BP) obtained by ambulatory blood pressure monitoring between 6 PM and 10 PM for placebo and graded-release diltiazem HCl extended release 120-mg, 240-mg, 360-mg PM, and 540-mg treatment groups. B) Least squares mean changes from baseline in diastolic BP and systolic BP obtained by ambulatory blood pressure monitoring between 5 AM and 12 noon for all treatment groups.

were significant ($P < .05$). Between the 360-mg AM and PM groups, the 24-h mean reductions in HR were not significant.

Safety Results

Overall, 216 (45.2%) patients in the GRD treatment groups and 34 (49.3%) from the placebo group reported AE/s during the double-blind treatment period of the study. At least one AE was reported by 182 (44.5%) of the GRD-treated patients, compared to 34 (49.3%) of the placebo-treated patients. Incidence of AEs were 34 (49.3%), 21 (31.3%), 29 (42.6%), 50 (49.0%), 52 (50.5%), and 30 (43.5%), respectively, for the placebo, 120-mg, 240-mg, 360-mg AM, 360-mg PM, and 540-mg treatment groups. There were no apparent trends in the incidence of AEs between the treatment groups (Table 3). Although the 540-mg dose was associated with the greatest reductions in SBP, DBP, and HR, the incidence of AEs observed was similar to that observed for the 240-mg treatment group, and lower than that observed for the placebo group. The most frequently occurring AEs reported previously overall for the combined GRD groups were similar to those reported for diltiazem,[17] and include headache (11.7%), upper respiratory tract infection (5.6%), and lower limb edema (5.4%). There were no episodes of bradycardia, and there were no episodes of first-degree atrioventricular

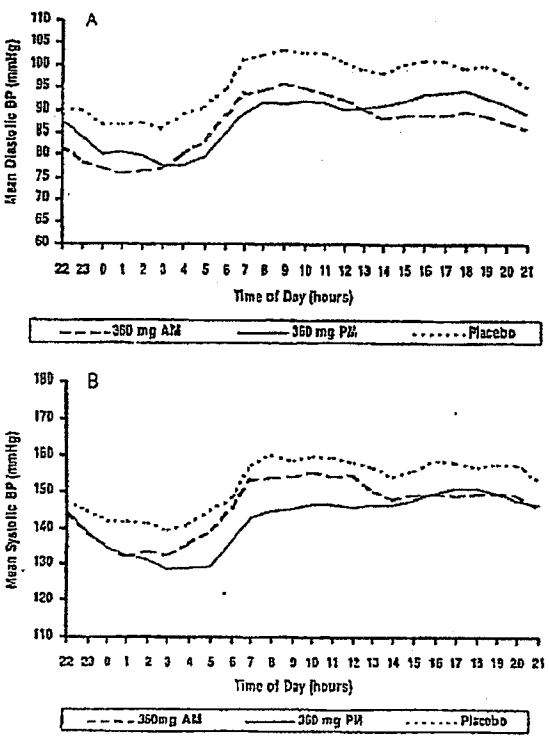

FIG. 2. The 24-h diastolic blood pressure (BP) (A) and systolic BP (B) profiles recorded by ambulatory blood pressure monitoring for placebo and graded-release diltiazem HCl extended release 360-mg AM and 360-mg PM treatment groups at the end of 7 weeks of double-blind treatment.

block requiring discontinuation from the study in the GRD treatment groups. Clinical laboratory abnormalities observed in the GRD groups were consistent with those reported previously in the approved package insert for diltiazem.[17]

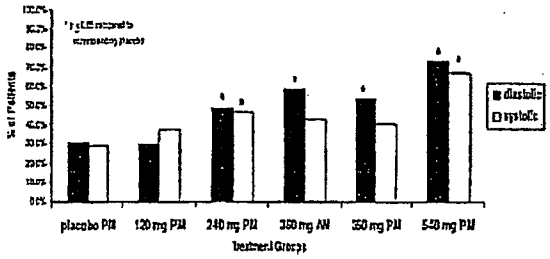

FIG. 3. Responder rates based on seated office diastolic and systolic BP measured at trough (6 PM ±1 h for PM dosing; 8 AM ±1 h for AM dosing) for all treatment groups. Diastolic BP responder rate was defined as the proportion of patients achieving a mean diastolic BP <90 mm Hg at end point or a decrease of at least 10 mm Hg from the baseline mean diastolic BP. Systolic BP responder rate was defined as the proportion of patients achieving a mean systolic BP <140 mm Hg at end point or a decrease of at least 10% from the baseline mean systolic BP.

Discussion

The results of this study clearly demonstrate that GRD, a novel graded-release diltiazem HCl extended-release formulation, designed for once-daily nighttime dosing, reduces BP over the 24-h dosing interval in a dose-dependent fashion. The antihypertensive effect for SBP and DBP were significant for doses above 120 mg/day. Nighttime administration of GRD 360 mg was associated with significantly greater reductions in DBP (−3.3 mm Hg) and SBP (−5.3 mm Hg), during the period 6 AM to 12 noon compared to the same dose administered in the morning. The 24-h BP profiles obtained at the end of the 7-week treatment period confirm that GRD synchronizes its antihypertensive effect with the circadian variation of BP. These results confirm GRD as a chronotherapeutic antihypertensive agent that maximizes its effect during the period of early morning BP surge, which coincides with the reported peak incidence of nonembolic stroke,[1,2] silent myocardial ischemia,[3,4] myocardial infarction,[1,5,6] and sudden cardiac death.[1,7,8] In addition, the smallest BP reduction occurred between 2 and 4 AM when BP is physiologically at its lowest level. The findings in this study confirm previous reports of a linear dose–response for the antihypertensive effects of different formulations of diltiazem over the dosage range 120 to 540 mg/day.[14,16,20] Furthermore, the high DBP response rate of 73% achieved in this study is similar to the 72% rate achieved for diltiazem in the VA Cooperative Study.[21,22] In addition, the sustained 24-h antihypertensive effect after once-daily administration, and the timing of its maximum effect at the time of abrupt increase of BP after arising from overnight sleep are desirable features of an optimal antihypertensive formulation described in Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI).[15]

Heart rate was similarly reduced in a dose-dependent fashion during the 24-h dosing interval in this study. The greatest reduction in HR occurred during the early morning post-awakening period. The combined reductions in SBP and HR may have beneficial clinical implications in reducing the SBP–HR product.[23,24] The latter is a well-recognized index of myocardial oxygen demand and has been shown to parallel silent myocardial ischemia.[25] In addition, the findings of the Framingham study reveal that the risk of developing cardiovascular disease in hypertensive patients and cardiovascular mortality increased in a continuous graded fashion with their accompanying increase in HR.[24,26] These findings and the fact that increased HR is an underappreciated accompaniment of hypertension, suggest that antihypertensive agents that reduce the HR may be particularly beneficial in reducing hypertensive cardiovascular mortality.[24]

The GRD was safe and very well tolerated across the dose range studied. Adverse events were qualitatively similar to those reported previously with other diltiazem formulations.[17] A most significant finding in this trial was

Table 3. Number (%) of the most frequently reported AE/s from the GRD and placebo treatment groups

Adverse Events	Placebo (*n* = 69)	GRD 120 mg (*n* = 67)	GRD 240 mg (*n* = 68)	GRD 360 mg AM (*n* = 102)	GRD 360 mg PM (*n* = 103)	GRD 540 mg (*n* = 69)
Headache NOS	10 (14.5)	8 (11.9)	10 (14.7)	13 (12.7)	11 (10.7)	6 (8.7)
Edema lower limb	4 (5.8)	2 (3.0)	4 (5.9)	8 (7.8)	3 (2.9)	5 (7.2)
Upper respiratory tract infection NOS	2 (2.9)	3 (4.5)	3 (4.4)	7 (6.9)	6 (5.8)	4 (5.8)
Nasopharyngitis	1 (1.4)	1 (1.5)	2 (2.9)	2 (2.0)	4 (3.9)	2 (2.9)
Constipation	1 (1.4)	0 (0.0)	0 (0.0)	2 (2.0)	1 (1.0)	2 (2.9)
Sinusitis NOS	2 (2.9)	1 (1.5)	0 (0.0)	2 (2.0)	2 (1.9)	0 (0.0)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.9)	1 (1.0)	1 (1.4)
Urinary tract infection NOS	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)

NOS = not otherwise specified; other abbreviations as in Tables 1 and 2.

despite a dose-dependent reduction in BP, no obvious dose-related trends in the incidence of AEs observed. In fact, although the 540-mg dose was associated with the greatest reductions in BP and HR, the incidence of AEs was similar to that observed for the 240-mg dose group and lower than that observed for the placebo group. These findings are important in light of a recent review of the anomalies in the dosing of diltiazem, which revealed that: 1) physicians routinely use subtherapeutic doses of diltiazem for treating hypertension for reasons based on the history of its development; 2) previous studies investigating the efficacy of diltiazem formulations showed that 360 mg/day was the most commonly required dose (by 85% of patients) for complete control of hypertension compared to 240 mg/day for angina; and 3) the *Physicians Desk Reference* (containing Food and Drug Administration-approved products) states that 180 to 240 mg/day is the usual starting dose for diltiazem and titration up to 540 mg/day may be carried out.[20] That review also revealed that in contrast, the prescribing patterns of physicians showed that prescriptions of diltiazem for the treatment of hypertension were most frequently for the 240-mg capsule (43.3%), followed by the 180-mg capsule (28.7%), 120-mg capsule (9.8%), and only a total of 4.0% for the 360-mg strength.[20] In this study, we have demonstrated that further increasing the dose of diltiazem to 540 mg impressively reduces BP with a safety profile no greater than for much smaller doses of diltiazem.

In conclusion, we have demonstrated that GRD, a novel chronotherapeutic agent, when dosed once-daily at nighttime in a dose-dependent fashion, effectively reduces BP over the 24-h dosing interval in patients with moderate-to-severe essential hypertension. Nighttime administration of GRD is associated with significant and clinically meaningful greater reductions in BP between 6 AM and 12 noon, the period of the early morning BP surge and clustering of adverse cardiovascular events, when compared to an identical morning dose. GRD was safe and well tolerated, and these results establish the 540-mg dose as another safe therapeutic option in patients with severe hypertension requiring additional BP control.

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Appendix:

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Teskin, Robin

From: Salim Mamajiwalla [salim.mamajiwalla@biovail.com]
Sent: Friday, January 28, 2005 4:55 PM
To: Teskin, Robin
Cc: Paul Maes
Subject: Polymethacrylates

Document.pdf (2 MB)

Robin,

I have attached a chapter out of the Hanbook of Pharmaceutical Sciences relating to polymethacrylates. The information Edith suggests we include can be found in Section 8.

-----Original Message-----
From: CA1 MFP - 3W [mailto:CA1MFP-3W@biovail.com]
Sent: Friday, January 28, 2005 5:02 PM
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Subject:

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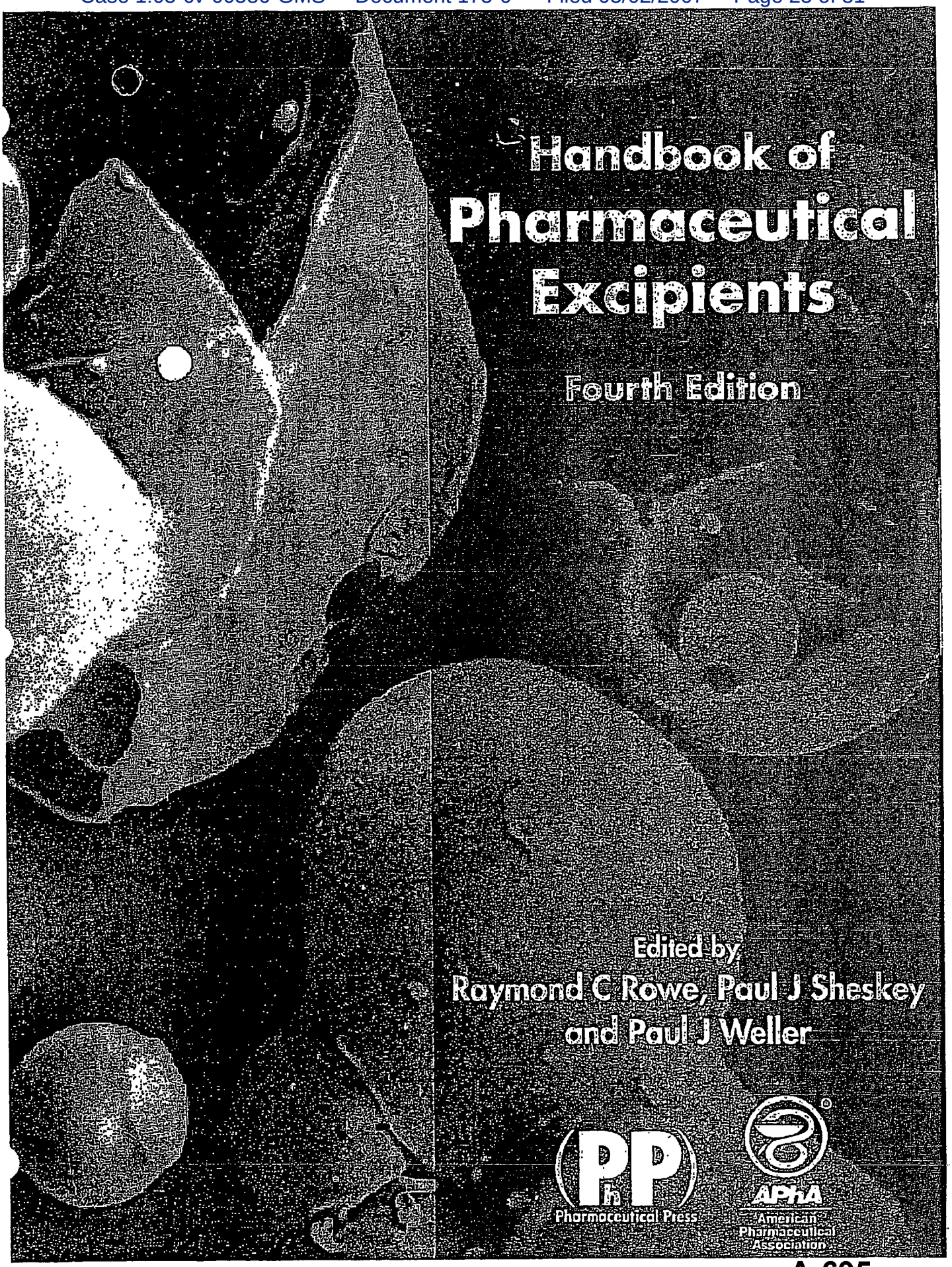
ANTICIPATION

The Examiner has rejected Claims 1-15, 17, 19-37, 39, 43, and 63-78 under 35 U.S.C. 102(b) as being anticipated by EPA 856313 (hereinafter "EPA '313"). The Examiner states that EPA '313 discloses a once daily product wherein the release rates overlap those claimed by Applicant. Applicant respectfully submits that all the independent claims as amended in the present application includes the limitation of a neutral copolymer as the at least one water insoluble swellable polymer. EPA '313 does not teach nor suggest the use of a neutral copolymer. The Examiner states that Claim 8 of EPA '313 broadly teaches the use of copolymers of acrylic and methacrylic esters, which would include the use of a neutral copolymer as the water insoluble polymer. However, Applicant respectfully submits that this teaching in EPA '313 does not include a neutral copolymer. All of the Eudragit-type polymeric materials taught in EPA '313 are charged polymers. Applicant has provided below a table of the Eudragit-type polymers and their corresponding charges. This information would have been known to the skilled artisan at the time of filing of the EPA '313 application.

Name	Charge
Eudragit RL	Cationic [ammonium]
Eudragit RS	Cationic [ammonium]
Eudragit L	Anionic [Carboxyl]
Eudragit S	Anionic [Carboxyl]
Eudragit E	Cationic [Diethyl amino]
Eudragit RL 30D	Cationic [ammonium]
Eudragit L 30D	Anionic [Carboxyl]
Eudragit E 12.5	Cationic [Diethyl amino]
Eudragit RL 12.5	Cationic [ammonium]
Eudragit RS 12.5	Cationic [ammonium]

Given that all of the Eudragit type polymers taught in EPA '313 are charged, Applicant submits that the skilled artisan, having read EPA' 313 in its entirety would

N



Handbook of Pharmaceutical Excipients

Fourth Edition

Edited by
Raymond C Rowe, Paul J Sheskey
and Paul J Weller

Pharmaceutical Press
APhA American Pharmaceutical Association

Published by the Pharmaceutical Press
Publications division of the Royal Pharmaceutical Society of Great Britain

1 Lambeth High Street, London SE1 7JN, UK
100 South Atkinson Road, Suite 206, Grayslake, IL 60030-7820, USA

and the American Pharmaceutical Association
2215 Constitution Avenue NW, Washington, DC 20037-2985, USA

First edition published 1986
Second edition published 1994
Third edition published 2000
Fourth edition published 2003

Text design by Barker Hilsdon, Lyme Regis
Typeset by Bibliocraft Ltd, Dundee
Printed in Great Britain by The Bath Press, Bath

ISBN 0 85369 472 9 (UK)
ISBN 1 58212 022 6 (USA)

A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
Handbook of pharmaceutical excipients.–4th ed. / edited by Raymond C. Rowe, Paul J. Sheskey, Paul J. Weller.
p. ; cm.
Includes bibliographical references and index.
ISBN 1-58212-022-6 (alk. paper) – ISBN 0-85369-472-9 (alk. paper)
1. Excipients–Handbooks, manuals, etc.
[DNLM: 1. Excipients–Handbooks. QV 735 H236 2003] I. Rowe, Raymond C. II. Sheskey, Paul J. III. Weller, Paul J.

RS201.E87H36 2003
615'.19–dc21

2003002641

Polymethacrylates

1 Nonproprietary Names

BP: Methacrylic acid–ethyl acrylate copolymer (1 : 1)
Methacrylic acid–ethyl acrylate copolymer (1 : 1) dispersion 30 per cent
Methacrylic acid–methyl methacrylate copolymer (1 : 1)
Methacrylic acid–methyl methacrylate copolymer (1 : 2)

PhEur: Acidum methacrylicum et ethylis acrylas polymerisatum 1 : 1
Acidum methacrylicum et ethylis acrylas polymerisatum 1 : 1 dispersio 30 per centum
Acidum methacrylicum et methylis methacrylas polymerisatum 1 : 1
Acidum methacrylicum et methylis methacrylas polymerisatum 1 : 2

USPNF: Ammonio methacrylate copolymer
Methacrylic acid copolymer
Methacrylic acid copolymer dispersion

Note that three separate monographs applicable to polymethacrylates are contained in the USPNF 20; *see* Section 9. Several different types of material are defined in the monographs. The PhEur 2002 contains four separate monographs applicable to polymethacrylates.

2 Synonyms

Eastacryl 30D; *Eudragit*; *Kollicoat MAE 30 D*; *Kollicoat MAE 30 DP*; polymeric methacrylates.

3 Chemical Name and CAS Registry Number

See Table I.

4 Empirical Formula and Molecular Weight

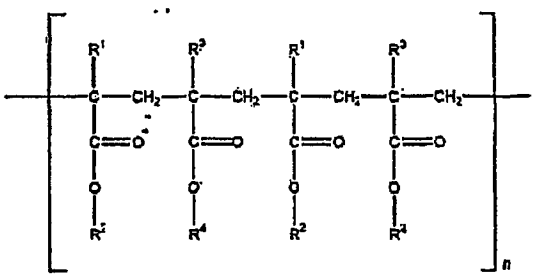
The PhEur 2002 describes methacrylic acid–ethyl acrylate copolymer (1 : 1) as a copolymer of methacrylic acid and ethyl acrylate having a mean relative molecular mass of about 250 000. The ratio of carboxylic groups to ester groups is about 1 : 1. It may contain suitable surfactants such as sodium dodecyl sulfate or polysorbate 80. An aqueous 30% w/v dispersion of this material is also defined in a separate monograph. Methacrylic acid–methyl methacrylate copolymer (1 : 1) is described in the PhEur 2002 as a copolymer of methacrylic acid and methyl methacrylate having a mean relative molecular mass of about 135 000. The ratio of carboxylic acid to ester groups is about 1 : 1. A further monograph in the PhEur 2002 describes methacrylic acid–methyl methacrylate copolymer (1 : 2), where the ratio of carboxylic acid to ester groups is about 1 : 2.

The USPNF 20 describes methacrylic acid copolymer as a fully polymerized copolymer of methacrylic acid and an acrylic or methacrylic ester. Three types, Type A, Type B, and Type C, are defined in the monograph. They vary in their methacrylic acid content and solution viscosity. Type C may contain suitable surface-active agents. Two additional polymers, Type A (*Eudragit RL*) and Type B (*Eudragit RS*), also referred to as ammonio methacrylate copolymers, consisting of fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, are also described in the USPNF 20. A further monograph for an aqueous dispersion of Type C methacrylic acid copolymer is also defined.

See Section 9.

Typically, the molecular weight of the polymer is ≥ 100 000.

5 Structural Formula



For *Eudragit E*:
R^1, R^3 = CH_3
R^2 = $CH_2CH_2N(CH_3)_2$
R^4 = CH_3, C_4H_9

For *Eudragit L* and *Eudragit S*:
R^1, R^3 = CH_3
R^2 = H
R^4 = CH_3

For *Eudragit RL* and *Eudragit RS*:
R^1 = H, CH_3
R^2 = CH_3, C_2H_5
R^3 = CH_3
R^4 = $CH_2CH_2N(CH_3)_3^+Cl^-$

For *Eudragit NE 30 D*:
R^1, R^3 = H, CH_3
R^2, R^4 = CH_3, C_2H_5

For *Eudragit L 30 D-55* and *Eudragit L 100-55*, *Eastacryl 30D*, *Kollicoat MAE 30 D* and *Kollicoat MAE 30 DP*:
R^1, R^3 = H, CH_3
R^2 = H
R^4 = CH_3, C_2H_5

6 Functional Category

Film former; tablet binder; tablet diluent.

7 Applications in Pharmaceutical Formulation or Technology

Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents.[1–15] Depending on the type of polymer used, films of different solubility characteristics can be produced; *see* Table II.

Table I: Chemical name and CAS Registry Number of polymethacrylates.

Chemical name	Trade name	Company name	CAS number
Poly(butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) 1:2:1	*Eudragit E 100*	Röhm GmbH	[24938-16-7]
	Eudragit E 12.5	Röhm GmbH	
Poly(ethyl acrylate, methyl methacrylate) 2:1	*Eudragit NE 30 D* (formerly *Eudragit 30 D*)	Röhm GmbH	[9010-88-2]
Poly(methacrylic acid, methyl methacrylate) 1:1	*Eudragit L 100*	Röhm GmbH	[25806-15-1]
	Eudragit L 12.5	Röhm GmbH	
	Eudragit L 12.5 P	Röhm GmbH	
Poly(methacrylic acid, ethyl acrylate) 1:1	*Eudragit L 30 D-55*	Röhm GmbH	[25212-88-8]
	Eudragit L 100-55	Röhm GmbH	
	Eastacryl 30D	Eastman Chemical	[25212-88-8]
	Kollicoat MAE 30 D	BASF Fine Chemicals	[25212-88-8]
	Kollicoat MAE 30 DP	BASF Fine Chemicals	
Poly(methacrylic acid, methyl methacrylate) 1:2	*Eudragit S 100*	Röhm GmbH	[25086-15-1]
	Eudragit S 12.5	Röhm GmbH	
	Eudragit S 12.5 P	Röhm GmbH	
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2	*Eudragit RL 100*		[33434-24-1]
	Eudragit RL PO	Röhm GmbH	
	Eudragit RL 30 D	Röhm GmbH	
	Eudragit RL 12.5	Röhm GmbH	
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1	*Eudragit RS 100*		[33434-24-1]
	Eudragit RS PO	Röhm GmbH	
	Eudragit RS 30 D	Röhm GmbH	
	Eudragit RS 12.5	Röhm GmbH	

Eudragit E is used as a plain or insulating film former; it is soluble in gastric fluid below pH 5. In contrast, *Eudragit L* and *S* types are used as enteric coating agents because they are resistant to gastric fluid. Different types are available that are soluble at different pH values: e.g., *Eudragit L 100* is soluble at pH > 6; *Eudragit S 100* is soluble at pH > 7.

Eudragit RL, *RS*, and *NE 30 D* are used to form water-insoluble film coats for sustained-release products. *Eudragit RL* films are more permeable than those of *Eudragit RS*, and films of varying permeability can be obtained by mixing the two types together.

Eudragit L 30 D-55 is used as an enteric coating film former for solid-dosage forms. The coating is resistant to gastric juice but dissolves readily at above pH 5.5.

Eudragit L 100-55 is an alternative to *Eudragit L 30 D-55*. It is commercially available as a redispersible powder.

Eastacryl 30D, *Kollicoat MAE 30 D*, and *Kollicoat MAE 30 DP*, are aqueous dispersions of methacrylic acid-ethyl acrylate copolymers. They are also used as enteric coatings for solid-dosage forms.

Polymethacrylates are also used as binders in both aqueous and organic wet-granulation processes. Larger quantities (5–20%) of dry polymer are used to control the release of an active substance from a tablet matrix. Solid polymers may be used in direct-compression processes in quantities of 10–50%.

Polymethacrylate polymers may additionally be used to form the matrix layers of transdermal delivery systems and have also been used to prepare novel gel formulations for rectal administration.[16]

See also Section 18.

8 Description

Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. Several different types are commercially available and may be obtained as the dry powder, as an aqueous dispersion, or as an organic solution. A (60:40) mixture of acetone and propan-2-ol is most commonly used as the organic solvent. *See* Tables I and III.

Eudragit E is cationic polymer based on dimethylaminoethyl methacrylate and other neutral methacrylic acid esters. It is soluble in gastric fluid as well as in weakly acidic buffer solutions (up to pH ≈ 5). *Eudragit E* is available as a 12.5% ready-to-use solution in propan-2-ol–acetone (60:40). It is light yellow in color with the characteristic odor of the solvents. Solvent-free granules contain ≈98% dried weight content of *Eudragit E*.

Eudragit L and *S*, also referred to as methacrylic acid copolymers in the USPNF 20 monograph, are anionic copolymerization products of methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester is approximately 1:1 in *Eudragit L* and approximately 1:2 in *Eudragit S*. Both polymers are readily soluble in neutral to weakly alkaline conditions (pH 6–7) and form salts with alkalis, thus affording film coats that are resistant to gastric media but soluble in intestinal fluid. They are available as a 12.5% solution in propan-2-ol without plasticizer (*Eudragit L 12.5* and *S 12.5*); and as a 12.5% ready-to-use solution in propan-2-ol with 1.25% dibutyl phthalate as plasticizer (*Eudragit L 12.5 P* and *S 12.5 P*). Solutions are colorless, with the characteristic odor of the solvent. *Eudragit L-100* and *Eudragit S-100* are white free-flowing powders with at least 95% of dry polymers.

Table II: Summary of properties and uses of commercially available polymethacrylates.

Type	Supply form	Polymer dry weight content	Recommended solvents or diluents	Solubility	Applications
Eudragit (Röhm GmbH)					
Eudragit E 12.5	Organic solution	12.5%	Acetone, alcohols	Soluble in gastric fluid to pH 5	Film coating
Eudragit E 100	Granules	98%	Acetone, alcohols	Soluble in gastric fluid to pH 5	Film coating
Eudragit L 12.5 P	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
Eudragit L 12.5	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
Eudragit L 100	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
Eudragit L 100-55	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Eudragit L 30 D-55	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Eudragit S 12.5 P	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
Eudragit S 12.5	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
Eudragit S 100	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
Eudragit RL 12.5	Organic solution	12.5%	Acetone, alcohols	High permeability	Sustained release
Eudragit RL 100	Granules	97%	Acetone, alcohols	High permeability	Sustained release
Eudragit RL PO	Powder	97%	Acetone, alcohols	High permeabi	Sustained release
Eudragit RL 30 D	Aqueous dispersion	30%	Water	High permeabi	Sustained release
Eudragit RS 12.5	Organic solution	12.5%	Acetone, alcohols	Low permeability	Sustained release
Eudragit RS 100	Granules	97%	Acetone, alcohols	Low permeability	Sustained release
Eudragit RS PO	Powder	97%	Acetone, alcohols	Low permeability	Sustained release
Eudragit RS 30 D	Aqueous dispersion	30%	Water	Low permeability	Sustained release
Eudragit NE 30 D	Aqueous dispersion	30% or 40%	Water	Swellable, permeable	Sustained release, tablet matrix
Eastacryl (Eastman Chemical Company)					
Eastacryl 30 D	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Kollicoat (BASF Fine Chemicals)					
Kollicoat 30 D	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Kollicoat 30 DP	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings

Note: Recommended plasticizers for the above polymers include dibutyl phthalate, polyethylene glycols, triethyl citrate, triacetin, and 1,2-propylene glycol. The recommended concentration of the plasticizer is approximately 10–25% plasticizer (based on the dry polymer weight). A plasticizer is not necessary with *Eudragit E 12.5*, *Eudragit E 100* and *Eudragit NE 30 D*.

Eudragit RL and *Eudragit RS*, also referred to as ammonio methacrylate copolymers in the USPNF 20 monograph, are copolymers synthesized from acrylic acid and methacrylic acid esters, with *Eudragit RL* (Type A) having 10% of functional quaternary ammonium groups and *Eudragit RS* (Type B) having 5% of functional quaternary ammonium groups. The ammonium groups are present as salts and give rise to pH-independent permeability of the polymers. Both polymers are water-insoluble, and films prepared from *Eudragit RL* are freely permeable to water, whereas, films prepared from *Eudragit RS* are only slightly permeable to water. They are available as 12.5% ready-to-use solutions in propan-2-ol–acetone (60 : 40). Solutions are colorless or slightly yellow in color, and may be clear or slightly turbid; they have an odor characteristic of the solvents. Solvent-free granules (*Eudragit RL 100* and *Eudragit RS 100*) contain ≥97% of the dried weight content of the polymer.

Eudragit RL PO and *Eudragit RS PO* are fine, white powders with a slight aminelike odor. They are characteristically the same polymers as *Eudragit RL* and *RS*. They contain ≥97% of dry polymer.

Eudragit RL 30 D and *Eudragit RS 30 D* are aqueous dispersions of copolymers of acrylic acid and methacrylic acid esters with a low content of quaternary ammonium groups. The dispersions contain 30% polymer. The quaternary groups occur as salts and are responsible for the permeability of films made from these polymers. Films prepared from *Eudragit RL 30 D* are readily permeable to water and to dissolved active substances, whereas films prepared from *Eudragit RS 30 D* are less permeable to water. Film coatings prepared from both polymers give pH-independent release of active substance. Plasticizers are usually added to improve film properties.

Table III: Solubility of commercially available polymethacrylates in various solvents.

Type	Solvent						
	Acetone and alcohols[a]	Dichloromethane	Ethyl acetate	1N HCl	1N NaOH	Petroleum ether	Water
Eudragit (Röhm GmbH)							
Eudragit E 12.5	M	M	M	M	–	M	–
Eudragit E 100	S	S	S	–	–	I	I
Eudragit L 12.5 P	M	M	M	–	M	P	P
Eudragit L 12.5	M	M	M	–	M	P	P
Eudragit L 100-55	S	I	I	–	S	I	I
Eudragit L 100	S	I	I	–	S	I	I
Eudragit L 30 D-55[b]	M[c]	–	–	M[d]	–	M	
Eudragit S 12.5 P	M	M	M	–	M	P	P
Eudragit S 12.5	M	M	M	–	M	P	P
Eudragit S 100	S	I	I	–	S	I	I
Eudragit RL 12.5	M	M	M	–	–	P	M
Eudragit RL 100	S	S	S	–	–	I	I
Eudragit RL PO	S	S	S	–	I	I	I
Eudragit RL 30 D	M[e]	M	M	–	I	I	M
Eudragit RS 12.5	M	M	M	–	–	P	M
Eudragit RS 100	S	S	S	–	–	I	I
Eudragit RS PO	S	S	S	–	I	I	I
Eudragit RS 30 D	M[e]	M	M	–	I	I	M
Eastacryl (Eastman Chemical Company)							
Eastacryl 30D[b]	M[c]	–	–	–	M[d]	–	M
Kollicoat (BASF Fine Chemicals)							
Kollicoat MAE 30 D[b]	M[c]	–	–	–	M[d]	–	M
Kollicoat MAE 30 DP[b]	M[c]	–	–	–	M[d]	–	M

S = soluble; M = miscible; I = insoluble or immiscible; P = precipitates.

[a] Alcohols including ethanol, methanol, and propan-2-ol.

[b] Supplied as a milky-white aqueous dispersion.

[c] A 1:5 mixture forms a clear, viscous, solution.

[d] A 1:2 mixture forms a clear or slightly opalescent, viscous liquid.

1 part of *Eudragit RL 30 D* or of *Eudragit RS 30 D* dissolves completely in 5 parts acetone, ethanol, or propan-2-ol to form a clear or slightly turbid solution. However, when mixed in a ratio of 1:5 with ethanol, *Eudragit RL 30 D* dissolves completely, whereas *Eudragit RS 30 D* dissolves only partially.

Eudragit NE 30 D is an aqueous dispersion of a neutral copolymer consisting of polymethacrylic acid esters. The dispersions are milky-white liquids of low viscosity and have a weak aromatic odor. Films prepared from the l[illegible]er swell in water, to which they become permeable. [illegible], films produced are insoluble in water, but give pH-independent drug release.

Eudragit L 30 D-55, is an aqueous dispersion of an anionic copolymer based on methacrylic acid and ethyl acrylate. The copolymer corresponds to USPNF 20 methacrylic acid copolymer, Type C. The ratio of free-carboxyl groups to ester groups is 1:1. Films prepared from the copolymers dissolve above pH 5.5, forming salts with alkalis, thus affording coatings that are insoluble in gastric media but soluble in the small intestine.

Eastacryl 30D, *Kollicoat MAE 30 D*, and *Kollicoat MAE 30 DP* are also aqueous dispersions of the anionic copolymer based on methacrylic acid and ethyl acrylate. The copolymer also corresponds to USPNF 20 methacrylic acid copolymer, Type C. The ratio of free-carboxyl groups to ester groups is 1:1. Films prepared from the copolymers dissolve above pH 5.5, forming salts with alkalis, thus affording coatings that are insoluble in gastric media, but soluble in the small intestine.

Eudragit L 100-55 (prepared by spray-drying *Eudragit L 30 D-55*) is a white, free-flowing powder that is redispersible in water to form a latex that has properties similar to those of *Eudragit L 30 D-55*.

9 Pharmacopeial Specifications

Specifications for polymethacrylates from the PhEur 2002 are shown in Table IV and those from the USPNF 20 in Table V.

10 Typical Properties

Acid value:
- 300–330 for *Eudragit L 12.5*, *L 12.5 P*, *L 100*, *L 30 D-55*, *L 100-55*; *Eastacryl 30D*; *Kollicoat MAE 30 D*, and *Kollicoat MAE 30 DP*
- 180–200 for *Eudragit S 12.5*, *S 12.5 P*, and *S 100*

Alkali value:
- 162–198 for *Eudragit E 12.5* and *E 100*
- 23.9–32.3 for *Eudragit RL 12.5*, *RL 100*, and *RL PO*
- 27.5–31.7 for *Eudragit RL 30 D*
- 12.1–18.3 for *Eudragit RS 12.5*, *RS 100*, and *RS PO*
- 16.5–22.3 for *Eudragit RS 30 D*

Density (bulk): 0.390 g/cm^3

Density (tapped): 0.424 g/cm^3

Table IV: Specifications from PhEur 2002.

Test	PhEur 2002			
	Methacrylic acid–ethyl acrylate copolymer (1:1)	Methacrylic acid–ethyl acrylate copolymer (1:1) dispersion 30%	Methacrylic acid–methyl methacrylate copolymer (1:1)	Methacrylic acid–methyl methacrylate copolymer (1:2)
Identification	+	+	+	+
Characters	+	+	+	+
Appearance of a film	+	+	+	+
Apparent viscosity	+	≤15 mPa s	50–200 mPa s	—
Particulate matter	—	≤1.0%	—	—
Ethyl acrylate and methacrylic acid	≤0.1%	≤0.1%	—	—
Methyl methacrylate and methacrylic acid	—	—	≤0.1%	≤0.1%
Residue on evaporation	—	28.5–31.5%	—	—
Loss on drying	≤5.0%	—	≤5.0%	≤5.0%
Sulfated ash	≤0.4%	≤0.2%	≤0.1%	≤0.1%
Microbial contamination	—	+	—	—
Assay (methacrylic acid units)	46.0–50.6%	46.0–50.6%	46.0–50.6%	27.6–30.7%

Density (true):
0.811–0.821 g/cm^3 for *Eudragit E*
0.83–0.85 g/cm^3 for *Eudragit L, S 12.5* and *12.5 P*
0.831–0.852 g/cm^3 for *Eudragit L, S 100*
1.062–1.072 g/cm^3 for *Eudragit L 30 D-55*
0.821–0.841 g/cm^3 for *Eudragit L 100-55*
0.816–0.836 g/cm^3 for *Eudragit RL* and *RS 12.5*
0.816–0.836 g/cm^3 for *Eudragit RL* and *RS PO*
1.047–1.057 g/cm^3 for *Eudragit RL* and *RS 30 D*
1.037–1.047 g/cm^3 for *Eudragit NE 30D*
1.062–1.072 g/cm^3 for *Eastacryl 30D*
1.062–1.072 g/cm^3 for *Kollicoat MAE 30 D* and *Kollicoat MAE 30 DP*

Refractive index:
n_D^{20} = 1.38–1.385 for *Eudragit E*
n_D^{20} = 1.39–1.395 for *Eudragit L* and *S*
n_D^{20} = 1.387–1.392 for *Eudragit L 100-55*
n_D^{20} = 1.38–1.385 for *Eudragit RL* and *RS*

Solubility: *see* Table II.

Viscosity (dynamic):
3–12 mPa s for *Eudragit E*
≤50 mPa s for *Eudragit NE 30D*
50–200 mPa s for *Eudragit L* and *S*
≤15 mPa s for *Eudragit L 30 D-55*
100–200 mPa s for *Eudragit L 100-55*
≤15 mPa s for *Eudragit RL* and *RS*
≤200 mPa s for *Eudragit RL* and *RS 30D*
≤15 mPa s for *Kollicoat MAE 30 D* and *Kollicoat MAE 30 DP*
145 mPa s for *Eastacryl 30D*

11 Stability and Storage Conditions

Dry powder polymer forms are stable at temperatures less than 30°C. Above this temperature, powders tend to form clumps, although this does not affect the quality of the substance and the clumps can readily be broken up. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 30°C.

Dispersions are sensitive to extreme temperatures and phase separation occurs below 0°C. Dispersions should therefore be stored at temperatures between 5 and 25°C and are stable for at least 18 months after shipping from the manufacturer's warehouse if stored in a tightly closed container at the above conditions.

12 Incompatibilities

Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and sc . For example, coagulation may be caused by soluble electro, tes, pH changes, some organic solvents, and extremes of temperature; *see* Table II. For example, dispersions of *Eudragit L 30 D*, *RL 30 D*, *L 100-55*, and *RS 30 D* are incompatible with magnesium stearate. *Eastacryl 30D*, *Kollicoat MAE 30 D*, and *Kollicoat MAE 30 DP* are also incompatible with magnesium stearate.

Interactions between polymethacrylates and some drugs can occur, although solid polymethacrylates and organic solutions are generally more compatible than aqueous dispersions.

13 Method of Manufacture

Prepared by the polymerization of acrylic and methacrylic acids or their esters, e.g., butyl ester or dimethylaminoethyl ester.

14 Safety

Polymethacrylate copolymers are widely used as film-coating materials in oral pharmaceutical formulations. They are also used in topical formulations and are generally regarded as nontoxic and nonirritant materials.

A daily intake of 2 mg/kg body-weight of *Eudragit* (equivalent to approximately 150 mg for an average adult) may be regarded as essentially safe in humans.

See also Section 15.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Additional measures should be taken when handling organic solutions of polymethacrylates. Eye protection, gloves, and a dust mask or respirator are recommended. Polymethacrylates should be handled in well-ventilated environment and measures should be taken to prevent dust formation.

Table V: Specifications from USPNF 20.

Test	USPNF 20	USPNF 20 (Suppl 1)
	Ammonio methacrylate copolymer[a]	Methacrylic acid copolymer
Identification	+	+
Viscosity		
Type A	≤15 mPa·s	50–200 mPa·s
Type B	≤15 mPa·s	50–200 mPa·s
Type C	–	100–200 mPa·s
loss on drying		
Type A	≤3.0%	≤5.0%
Type B	≤3.0%	≤5.0%
Type C	–	≤5.0%
Residue on ignition		
Type A	≤0.1%	≤0.1%
Type B	≤0.1%	≤0.1%
Type C	–	≤0.4%
Arsenic	–	≤2 ppm
Heavy metals	≤0.002%	≤0.002%
Organic volatile impurities	–	+
Limit of monomers	–	≤0.05%
Methyl methacrylate	≤0.005%	–
Ethyl acrylate	≤0.025%	–
Assay of methacrylic acid units (dried basis)		
Type A	8.85–11.96%	46.0–50.6%
Type B	4.48–6.77%	27.6–30.7%
Type C	–	46.0–50.6%

[a] Corresponds to Eudragit RL and RS.

Acute and chronic adverse effects have been observed in workers handling the related substances methyl methacrylate and poly(methyl methacrylate) (PMMA).[17,18] In the UK, the occupational exposure limit for methyl methacrylate has been set at 208 mg/m³ (50 ppm) long-term (8-hour TWA), and 416 mg/m³ (100 ppm) short-term.[19]

See also Section 17.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Methyl methacrylate; poly(methyl methacrylate).

Methyl methacrylate

Empirical formula: $C_5H_8O_2$
Molecular weight: 100.13
CAS number: [80-62-6]
Synonyms: methacrylic acid, methyl ester; methyl 2-methacrylate; methyl 2-methylpropenoate; MME.
Safety:
LD_{50} (dog, SC): 4.5 g/kg
LD_{50} (mouse, IP): 1 g/kg
LD_{50} (mouse, oral): 5.2 g/kg
LD_{50} (mouse, SC): 6.3 g/kg
LD_{50} (rat, IP): 1.33 g/kg
LD_{50} (rat, SC): 7.5 g/kg
Comments: methyl methacrylate forms the basis of acrylic bone cements used in orthopedic surgery.

Poly(methyl methacrylate)

Empirical formula: $(C_5H_8O_2)_n$
Synonyms: methyl methacrylate polymer; PMMA.
Comments: poly(methyl methacrylate) has been used as a material for intraocular lenses, for denture bases, and as a cement for dental prostheses.

18 Comments

A number of different polymethacrylates are commercially available that have different applications and properties; *see* Table II.

For spray coating, polymer solutions and dispersions should be diluted with suitable solvents. Some products need the addition of a plasticizer such as dibutyl sebacate, dibutyl phthalate, glyceryl triacetate, or polyethylene glycol. Different types of plasticizer may be mixed to optimize the polymer properties for special requirements.

19 Specific References

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20 General References

McGinity JW. *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*, 2nd edn. New York: Marcel Dekker, 1989.

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21 Authors

RK Chang, AJ Shukla.

22 Date of Revision

1 November 2002.

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ExAct

Excipients & Actives for Pharma

Kollicoat® SR 30 D

Coated drug delivery systems.

K. Kolter, S. Gebert

› Introduction

Sustained release dosage forms include single-unit and multiple-unit forms as well as coated forms and matrix forms [1]. Up to now, with the exception of the OROS System [2], the production of coated single-unit forms has been regarded as a malpractice, as the risk of dose dumping due to an incorrectly applied coating, or damage to a coating was too high. The OROS System is used in several products that are available on the market, but it has major disadvantages, such as the tricky operation of laser drilling, the use of organic solvents, high cost, and a low concentration of the drug in the core.

› Objective

The aim of this project was to develop a coated, sustained release single-unit form that is simple to manufacture and poses no risk of dose dumping.

› Experimental

Materials

Kollicoat® SR 30 D (polyvinyl acetate dispersion, BASF Aktiengesellschaft), metoprolol tartrate (Moehs S. A.).

Methods

Metoprolol tartrate was granulated with Kollidon® 30 solution, mixed with the other excipients for 10 minutes in a Turbula mixer, and compressed into tablets on a Korsch PH 106.

Tablet cores in batches of 5.0 kg were spray-coated with a pigmented Kollicoat® SR 30 D dispersion in a 24" Accela Cota

Mechanical testing of the tablets

The film-coated tablets were subjected to a friability test (500 revolutions, drop height 15.5 cm) in an Erweka Friabilator, allowed to fall 20 times from a height of 1.5 m, and pricked with a needle.

› Results and Discussion

From theoretical considerations, it is clear that a controlled release coating on a tablet must possess a high degree of flexibility, to ensure that any swelling of the core – whether in storage or during drug release – does not crack the film. It was found in tests on isolated films that polyvinyl acetate (Kollicoat® SR 30 D) has far greater elasticity than ethyl cellulose or ammonio methacrylate copolymer.

The permeability of the film coating can be adjusted by adding water-soluble or water-swellable substances, polymers if possible. As is to be expected, the release rate slows with increasing thickness of the coating. The release curve is S-shaped, as, initially, water has to penetrate the coating and enter the core in order to at least partially dissolve the drug substance before this can diffuse out through the coating. The time lag between first contact with water and drug release also depends on the thickness of the coating and the quantity of water-soluble excipients.

The coated tablets were subjected to strong mechanical stress.

Table 1: Core composition

Metoprolol tartrate	200.0 mg
Kollidon® 30	6.0 mg
Di-Tab	160.0 mg
Aerosil 200	3.0 mg
Talc	4.0 mg
Magnesium stearate	4.0 mg
Total tablet weight	391.5 mg

Table 2: Coating composition

Kollicoat® SR 30 D	43.5 %
Triacetin	0.7 %
Kollicoat® IR	3.3 %
Kollicon® 30	0.5 %
Titanium dioxide	0.5 %
Sicovit® Red (iron oxide), optional	0.5 %
Talc	3.5 %
Water	47.5 %
	100.0 %

Table 3: Coating parameters

Batch size	5.0 kg
Inlet air temperature	50 °C
Product temperature	35 °C
Atomizing pressure	2.0 bar
Spraying rate	22 g/min
Coating weight	4, 6, 8, 10 mg/cm²

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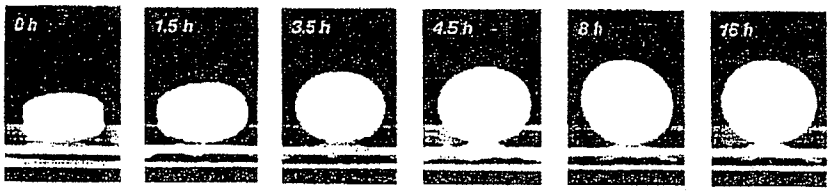
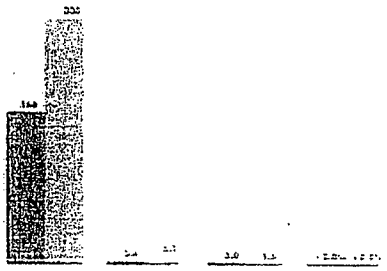
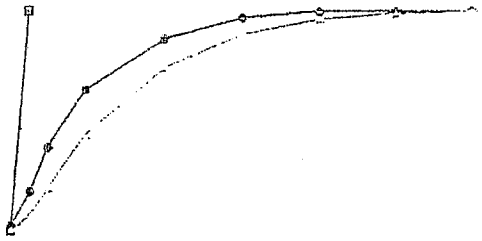


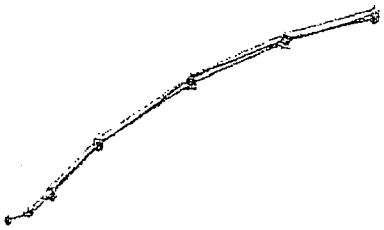
Neither a friability test (500 revolutions, 15.5 cm drop height) nor 20 drops from a height of 1.5 m had any noticeable effect on the release characteristics. Surprisingly, the film-coated tablets can even be pricked with a needle without affecting drug release. Kollidon® SR possesses enormous plasticity that ensures that small holes are self-sealing, particularly when the tablet is introduced into an aqueous medium. As a result, such coatings have a previously unknown self-repair mechanism.



with 5 % triacetin



cores
5 mg/cm² coating
9 mg/cm² coating



pH 6.8, 2 h
friability test
untreated

References

[1] M.N.V. Ravi Kumar and N. Kumar, Polymeric controlled drug delivery systems, Drug Dev. Ind. Pharm. 27, 1–30 (2001).
[2] S. Kettenhoit et al., Osmotic drug delivery system, German Patent Application 19747261 (1999).

Conclusions

- Film coatings based on Kollicoat® SR 30 D are very resistant to mechanical stress and possess a self-repair mechanism.
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Talc	3.5 %
Water	47.5 %
	100.0 %

Table 3:
Coating parameters

Batch size	5.0 kg
Inlet air temperature	50 °C
Product temperature	35 °C
Atomizing pressure	2.0 bar
Spraying rate	22 g/min
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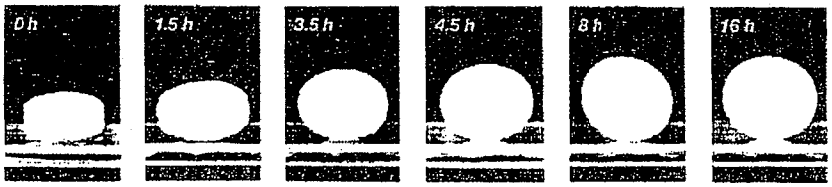

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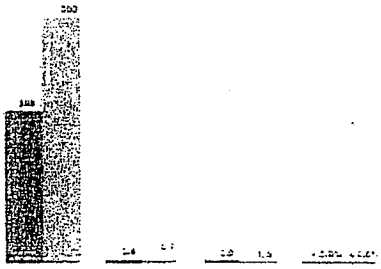
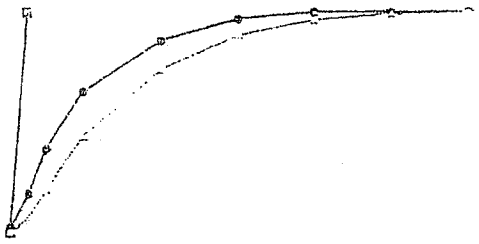
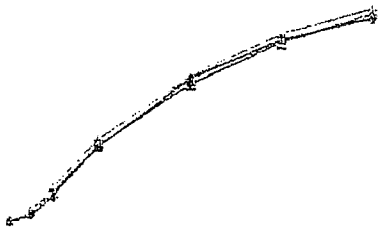


with 5 % triacetin



core
4 mg/cm² coating
8 mg/cm² coating



friability test
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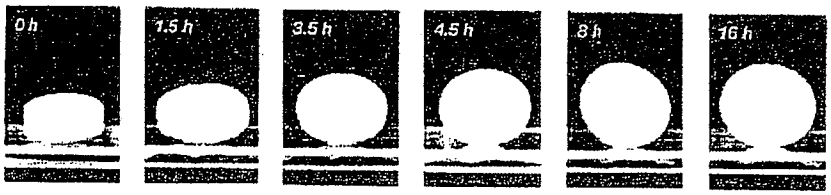
Titanium dioxide	0.5 %
Sicovit® Red (iron oxide), optional	0.5 %
Talc	3.5 %
Water	47.5 %
	100.0 %

Table 3: Coating parameters

Batch size	5.0 kg
Inlet air temperature	50 °C
Product temperature	35 °C
Atomizing pressure	2.0 bar
Spraying rate	22 g/min
Coating weight	4, 6, 8, 10 mg/cm²



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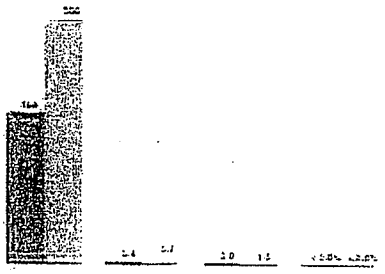

□ with 5% triacetin

References

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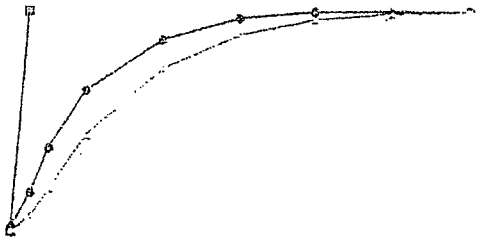

□ cores
◆ 4 mg/cm² coating
○ 6 mg/cm² coating

Conclusions

- Film coatings based on Kollicoat® SR 30 D are very resistant to mechanical stress and possess a self-repair mechanism.
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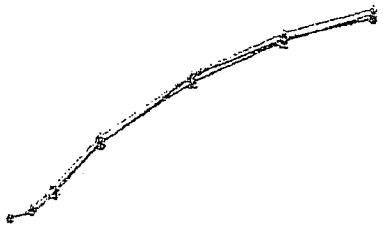


□ friability test
◆ untreated

P

Technical Information

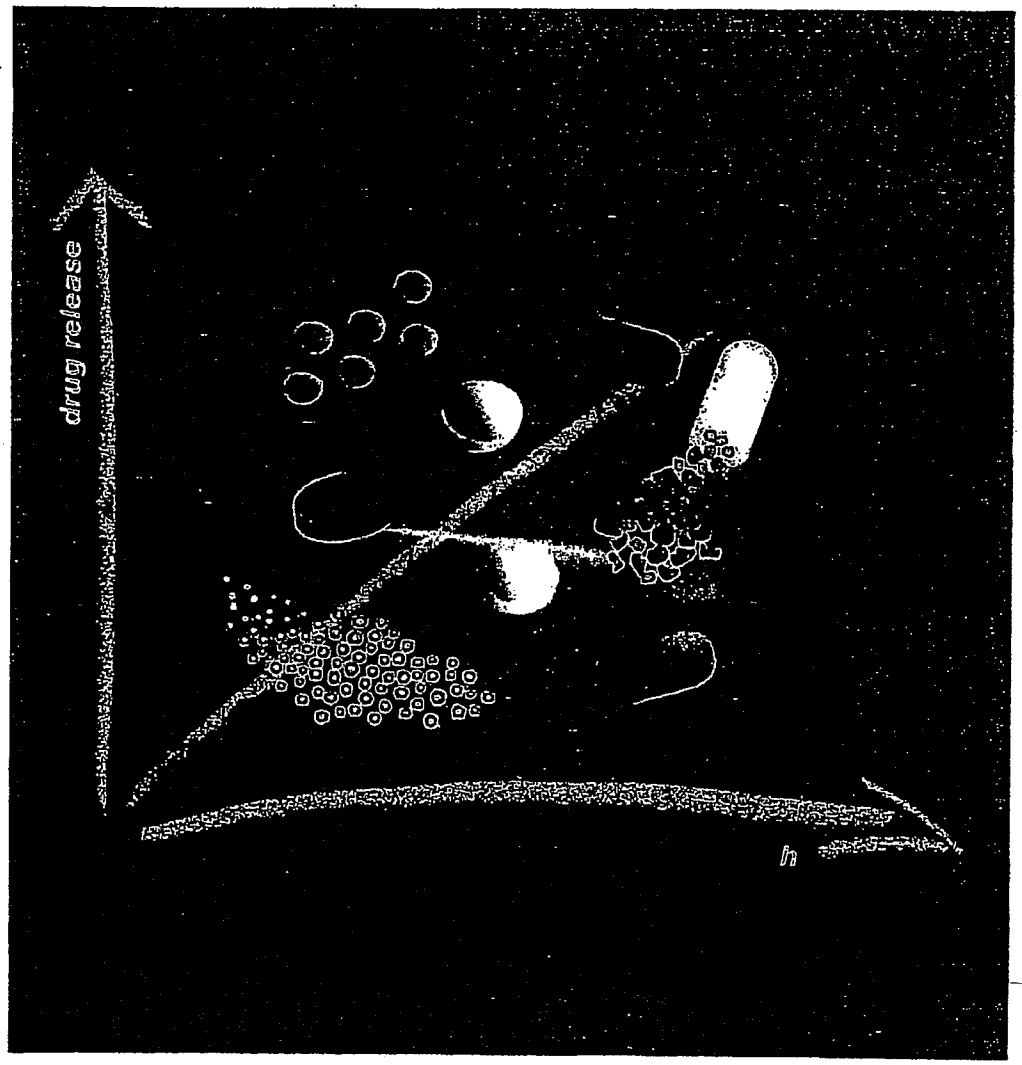
Kollicoat® SR 30 D

January 2004
Supersedes issue of June 1999

Register 2

® = Registered trademark of
BASF Aktiengesellschaft

Polyvinyl acetate dispersion for sustained-release pharmaceutical formulations



Contents

Microbiological status

Kollicoat® SR 30 D is not susceptible to microbial contamination. Microbiological testing is carried out in accordance with Ph. Eur., Category 3.

Unless otherwise stated, the methods of determination are taken from current European Pharmacopoeia.

2.3 Pharmacopoeia

A draft monograph Poly (Vinyl Acetate) Dispersion 30 per cent has been published in Pharmeuropa. Additionaly US-DMF was filed.

2.4 Marketing authorization

Polyvinyl acetate is described, with reference to oral administration, in Japanese Pharmaceutical Excipients (JPE) 1993. Polyvinyl acetate is used in a variety of medicinal products for oral administration in numerous countries including Germany, France and the USA.
Polyvinyl acetate is also used in the food industry, for example as a chewing gum base or for coating fruits and vegetables. It is listed, for example, in Germany in the Regulations for Marketing Authorization of Food Additives for Technological Purposes, in the USA in the Code of Federal Regulations, Section 172.615, in South Korea in the Public Code on Food Additives 1995 and in Japan in the Japanese Standard for Food Additives, March 1997.

3. Application and Processing

3.1 Application

Sustained-release coated formulations
Kollicoat® SR 30 D is used mainly for the manufacture of sustained-release dosage forms. Very effective control of drug release is achieved by coating pellets, granules and crystals.

Protective coats
Applied in small quantities or with hydrophilic additives, Kollicoat® SR 30 D provides good protection against odour or taste. It can also be used, for example as a subcoating, for isolating active ingredients to prevent interactions.

Sustained-release matrix formulations
Matrix tablets can be produced by granulating active ingredients, for example in the fluidized bed process, followed by compression.

3.2 Processing information

The dispersion is not particularly vulnerable to external influences. Nevertheless, the following factors could result in coagulate formation that precludes further use of the dispersion:

- addition of finely dispersed pigments
- high shear gradients in stirrers and mills
- addition of emulsifiers, stabilizers or wetting agents
- pH changes
- organic solvents
- foaming

The minimum film-forming temperature (MFT) of the pure dispersion is 18 °C. It can be lowered by adding plasticizers.

The dispersion can theoretically also be used without plasticizers; but these additives enhance film formation and the flexibility of the films.

The following are suitable as plasticizers or gloss enhancers:

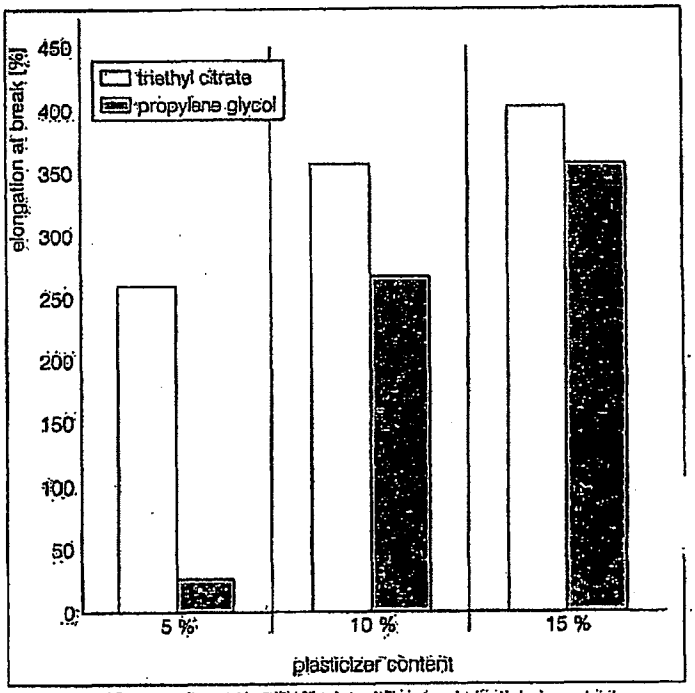
- 1,2-propylene glycol
- triethyl citrate
- polyethylene glycols and
- triacetin

The recommended plasticizer content is 0–10% with reference to the dried polymer substance

1,2-Propylene glycol offers advantages for processing the dispersion and for film properties.

Plasticizer supplement		MFT
2.5%	propylene glycol	18°C
5%	propylene glycol	16°C
10%	propylene glycol	14°C
15%	propylene glycol	12°C
2.5%	triethyl citrate	10°C
5%	triethyl citrate	8°C
10%	triethyl citrate	1°C
15%	triethyl citrate	< 0°C

Triethyl citrate lowers the MFT more than propylene glycol.
Kollicoat® SR 30 D films without plasticizer are relatively brittle in the dry state; when wet, however, they are very flexible (elongation at break > 100%).
A small plasticizer supplement also increases the flexibility of the polymer in the dry state. Elongation at break values of more than 250% can be achieved using 5% triethyl citrate or 10% propylene glycol. Crack formation in coats, due for example to pronounced swelling of the core, is thereby prevented.



Correlation of elongation at break of isolated films and plasticizer content

The permeability of the water-insoluble but swellable films can be varied by:

- the layer thickness of the coat
- the use of pore formers (Kollidon® VA 64, Kollidon® 30, HPMC, Avicel® PH 105). The required content depends on the desired release profile.

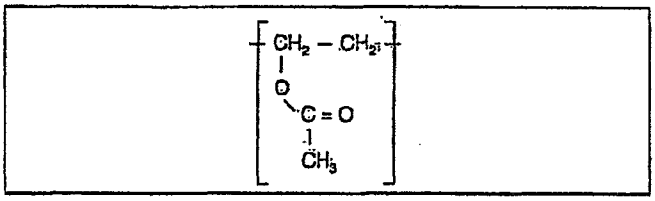
The layer thickness should not be less than 1.5 mg/cm² (= about 15 µm) since otherwise film defects and burst effects are to be expected.
Kollicoat® SR 30 D can be applied using either a top spray or bottom spray in the fluidized-bed coater.

1 Introduction

1.1 General

Kollicoat® SR 30 D is a polyvinyl acetate dispersion stabilized with povidone and sodium lauryl sulfate. The dispersion is suitable for the manufacture of pH-independent sustained-release formulations. The dispersion can also be used for taste masking.

1.2 Chemical structure



1.3 Trivial name

Poly (Vinyl Acetate) Dispersion 30 per cent

1.4 Commercial formulation

Kollicoat® SR 30 D is an aqueous dispersion with a solids content of 30%. The low viscosity product has a weak characteristic odour and a milky white or slightly yellowish appearance.

2 Specifications and properties

2.1 Description

The dispersion consists of about 27% polyvinyl acetate, 2.7% povidone and 0.3% sodium lauryl sulfate.

2.2 Physical and chemical properties

Identification:	Conforms
Film formation:	Conforms
Solubility:	Conforms
pH:	3.5–5.5
Relative density:	1.045–1.065
Viscosity	< 100 mPas
Coagulate content:	< 0.5%
Solids content:	28.5–31.5%
Sulfated ash:	< 0.5%.
Heavy metals:	< 20 ppm
Monomers:	< 100 ppm
Microbiological status:	Conforms

Solubility

Kollicoat® SR 30 D is miscible with water in any ratio while retaining its milky-white appearance. Mixing the product with ethanol or isopropyl alcohol in a 1 : 5 ratio produces a slightly turbid and somewhat viscous solution; a solution in acetone is more turbid. On addition of organic solvents the polymer precipitates out but then dissolves when further solvent is added.
Kollicoat® SR 30 D is insoluble in dilute alkaline or acidic solutions. The dispersion retains a milky-white appearance.

Film formation

10 g of Kollicoat® SR 30 D are mixed with 0.3 g of propylene glycol. When poured onto a glass plate, a colourless or faintly yellowish film forms after the liquid has evaporated.

Viscosity

Viscosity is determined in accordance with DIN EN ISO 3219 at a shear gradient of 250 sec^{-1} and 23 °C.

Coagulate content

100 g of the substance is filtered through a 90 µm sieve. The residue is dried to constant weight at 105 °C in a drying oven.

Whether curing (thermal postcoating treatment) is necessary to achieve storage-stable drug release characteristics, should be determined on a casewise basis. The good film-coating properties generally mean that the film coat is insensitive to curing. In many cases, therefore, curing is unnecessary.
Kollicoat® SR 30 D has no charged or ionizable groups and consequently results in pH-independent film coats.

Using talc in the spray formulations reduces the sticking tendency thereby preventing agglomeration of small particles in the fluidized bed as well as adhesion effects.
Mixing the coated particles with 0.1–0.5% Aerosil® 200 prevents cohesion during storage even at elevated temperatures.

4. Formulation examples

4.1 Theophylline sustained-release pellets

Composition of spray suspension

The formulation is designed for 500 g pellets (diameter 0.8–1.3 mm)
Pellets: Spherofilin (Kholl AG)

	Parts by weight [g]	Composition [%]
Polymer suspension		
Kollicoat® SR 30 D	223.67	50.0
Propylene glycol	6.71	1.5
Water	149.86	33.5
Pigment suspension		
Kollidon® 30	2.24	0.5
Titanium dioxide	2.24	0.5
Sicovit® Red 30	2.24	0.5
Talc	15.65	3.5
Water	44.73	10.0
	447.35	100.0

Preparation of spray suspension

Polymer suspension:
Propylene glycol followed by Kollicoat® SR 30 D are added to the stated quantity of water with stirring.

Pigment suspension:
Kollidon® 30 is dissolved in the stated quantity of water. Sicovit® Red 30, titanium dioxide and talc are added with vigorous stirring and the mixture is homogenized with a corundum disk mill.

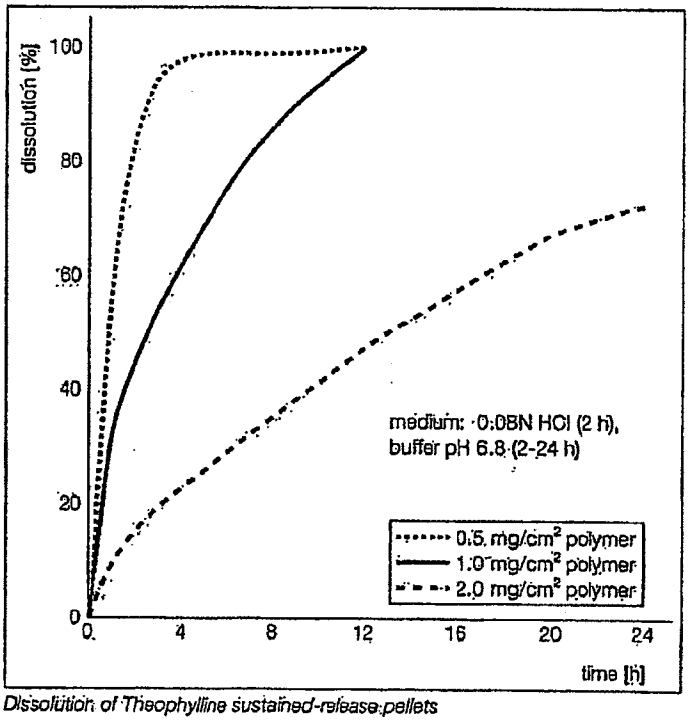
Spray suspension:
The pigment suspension is incorporated into the polymer suspension with stirring. The suspension must be stirred during the spray process to prevent settling.

Machine parameters

Machine	Aeromatic Strea-1 fluidized bed granulator
Batch size	500 g
Inlet air temperature	60°C
Outlet air temperature	37°C
Product temperature	38°C
Air flow	80 m³/h
Spraying pressure	1 bar
Spraying rate	11.5 g/min
Spraying time	39 min
Secondary drying	45°C/5 min
Coating level	2 mg film former/cm²

The spray suspension is sprayed continuously onto the fluidized, pre-heated pellets by the top spray method.

The coating level of 2 mg film former/cm² stated here was established for the pellets by surface area determination. Since the particle size distribution and surface structure influence the required polymer quantity, calculating the surface area is recommended as a means of estimating the required coating level in each specific case.



Dissolution of Theophylline sustained-release pellets

4.2 Caffeine sustained-release pellets

Composition of pellets: 10% caffeine, 43.75% Avicel® PH 101, 43.75% lactose, 2.5% Kollidon® VA 64

Composition of spray suspension: The formulation is designed for 500 g pellets (diameter 0.7–1.4 mm)

	Parts by weight [g]	Composition [%]
Polymer suspension		
Kollicoat® SR 30 D	269.44	49.3
Propylene glycol	8.09	1.5
Water	188.61	34.5
Pigment suspension		
Kollidon® 30	2.7	0.5
Titanium dioxide	2.7	0.5
Sicovit® Red 30	2.7	0.5
Talc	18.87	3.4
Water	53.89	9.8
	547.99	100.0

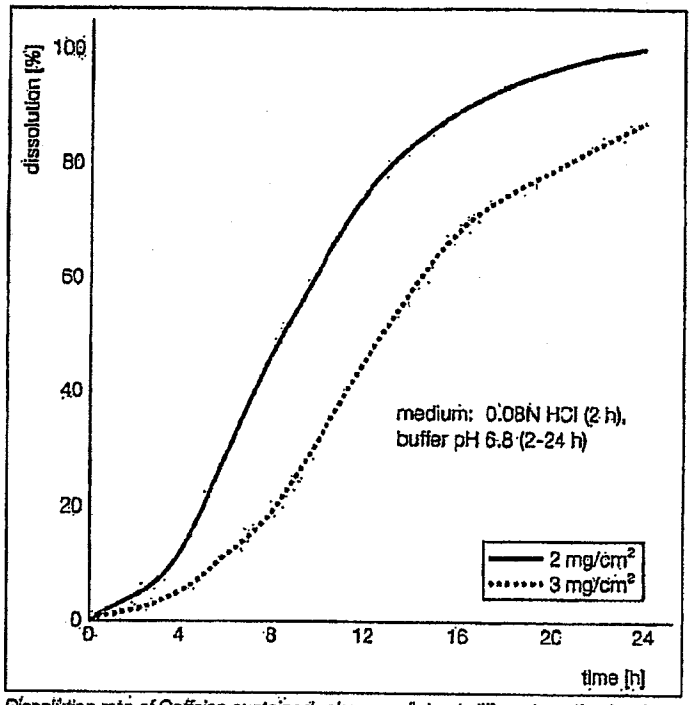
Preparation of spray suspension: *See Working Procedure 4.1*

Machine parameters:

Machine	Aeromatic Strea-1 fluidized bed granulator
Batch size	500 g
Inlet air temperature	60°C
Outlet air temperature	36°C
Product temperature	37°C
Air flow	80 m³/h
Spray pressure	1 bar
Spraying rate	12 g/min
Spraying time	45 min
Secondary drying	45°C/5 min
Coating level	3 mg film former/cm²

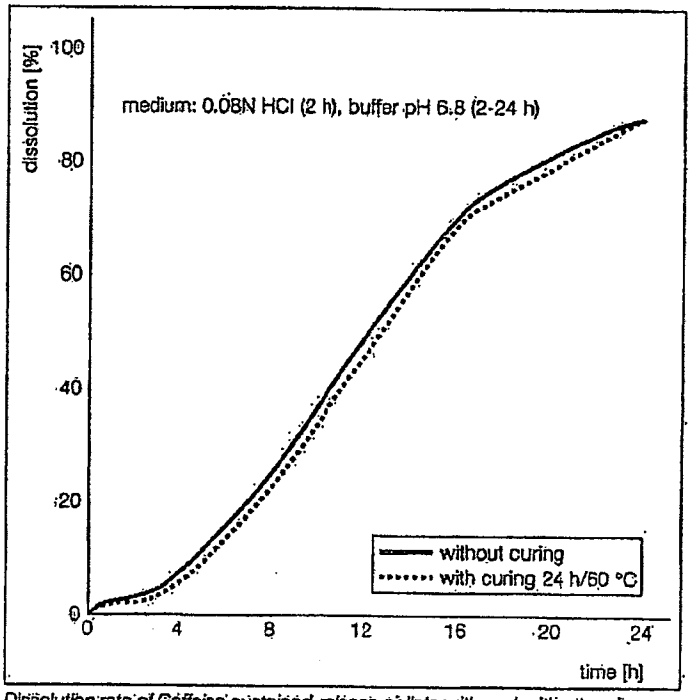
The spray suspension is sprayed continuously onto the fluidized, pre-heated pellets by the top-spray method.

The coating level of 3 mg film former/cm² stated here was established for the pellets by surface area determination. Since the particle size distribution and surface structure influence the required polymer quantity, calculating the surface area is recommended as a means of estimating the required coating level in each specific case.

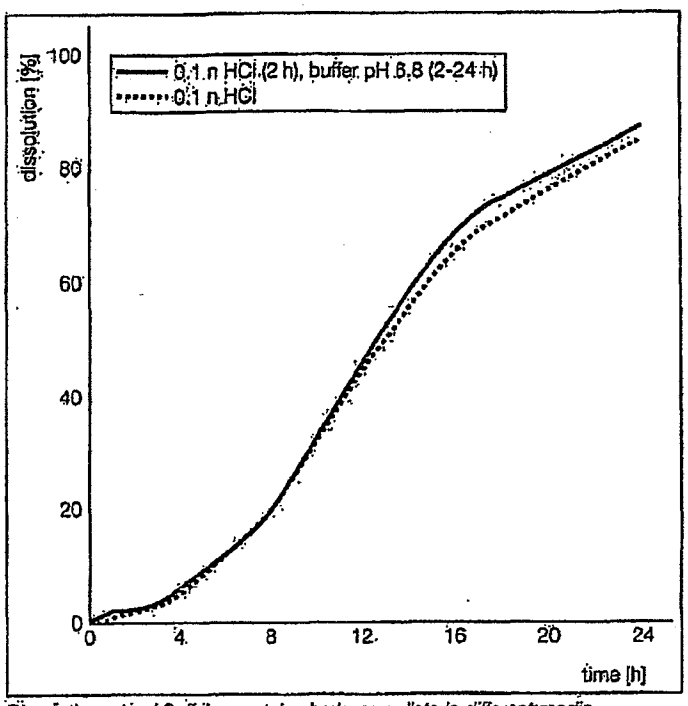


Dissolution rate of Caffeine sustained-release pellets at different coating levels

Curing (Thermal postcoating treatment) of the pellets is not necessary.



Dissolution rate of Caffeine sustained-release pellets with and without curing



Dissolution rate of Caffeine sustained-release pellets in different media

The release of caffeine pellets is pH independent.

4.3 Propanol sustained-release pellets

Composition of pellets: 20.0% propranolol, 51.66% Avicel® PH 101, 25.84% lactose, 2.5% Kollidon® VA 64

Composition of spray suspension

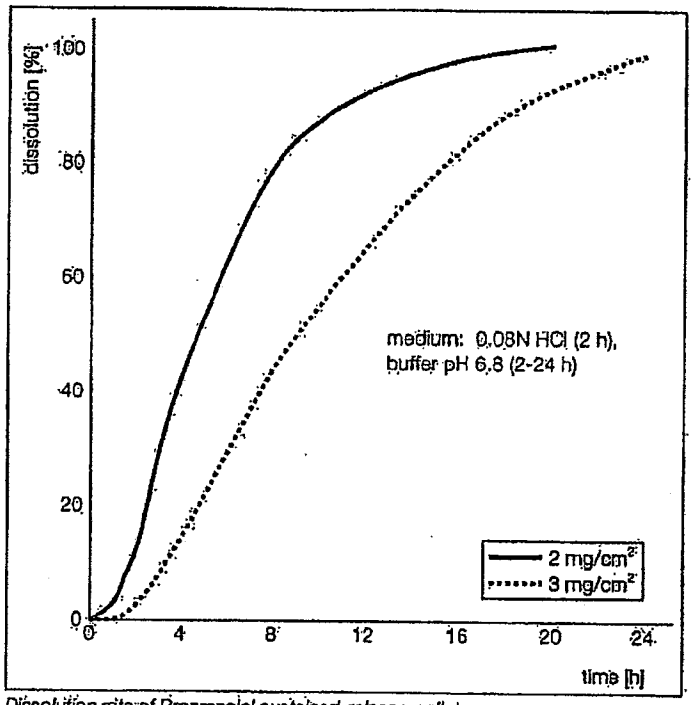
The formulation is designed for 500 g pellets (diameter 0.4–1.5 mm)

	Parts by weight [g]	Composition [%]
Polymer suspension		
Kollicoat® SR 30 D	249.41	49.2
Propylene glycol	7.49	1.5
Water	174.59	34.5
Talc suspension		
Talc	29.94	5.9
Water	44.91	8.9
	506.34	100.0

Preparation of spray suspension *See Working Procedure 4.1.*

Machine parameters

Machine	Aeromatic Strea-1 fluidized bed granulator
Batch size	500 g
Inlet air temperature	60°C
Outlet air temperature	35°C
Product temperature	36°C
Air flow	80 m³/h
Spraying pressure	1 bar
Spraying rate	13 g/min
Spraying time	39 min
Secondary drying	45°C/5 min
Coating level	3 mg film former/cm²



Dissolution rate of Propranolol sustained-release pellets.

4.4 Taste-masked acetaminophen

Acetaminophen granules, (Knoll AG)

Smaller quantities have to be applied for taste masking since otherwise drug release characteristics would be excessively altered.

Crystalline acetaminophen is coated with 4% Kollicoat® SR 30 D.

The formulation is designed for 500 g powder.

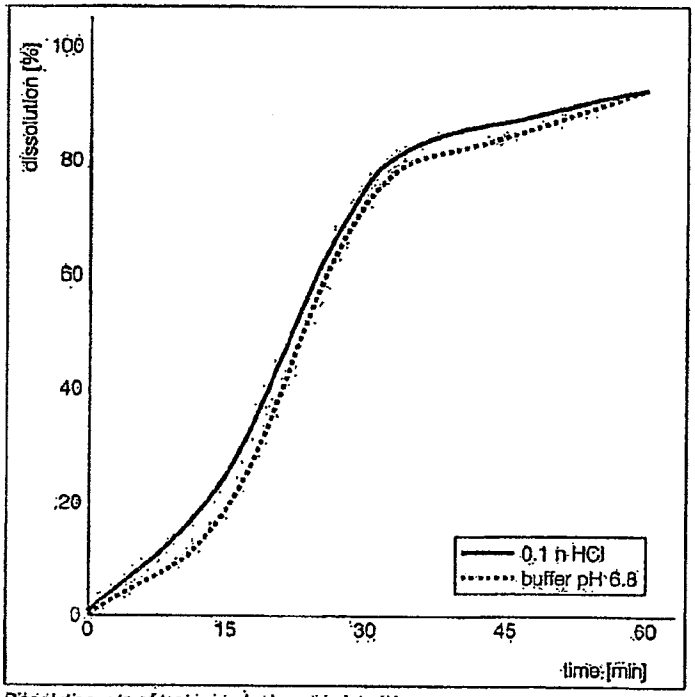
	Parts by weight [g]	Composition [%]
Polymer suspension		
Kollicoat® SR 30 D	73.33	100.0

Machine parameters

Machine	Aeromatic Strea-1 fluidized bed granulator
Batch size	500 g
Inlet air temperature	60°C
Outlet air temperature	40°C
Product temperature	41°C
Air flow	80 m³/h
Spraying pressure	1 bar
Spraying rate	9 g/min
Spraying time	9 min
Secondary drying	45°C/5 min
Coating level	4%

Taste masking

No bitter taste



Dissolution rate of taste-masked acetaminophen

5. Storage	Protect from frost and store at 20°C
6. Stability	At least 16 months in the unopened original container. On exposure to heat and frost and if foaming occurs, aqueous dispersions may form coagulates that preclude further use of the product.
7. PBG No.	10201076
8. Packaging	25-l polyethylene container. The product can also be filled into larger containers.
Note	The data submitted in this publication are based on our current knowledge and experience. They do not constitute a guarantee in the legal sense of the term and, in view of the manifold factors that may affect processing and application, do not relieve processors from the responsibility of carrying out their own tests and experiments. Any relevant patent rights and existing legislation and regulations must be observed.

Technical Information

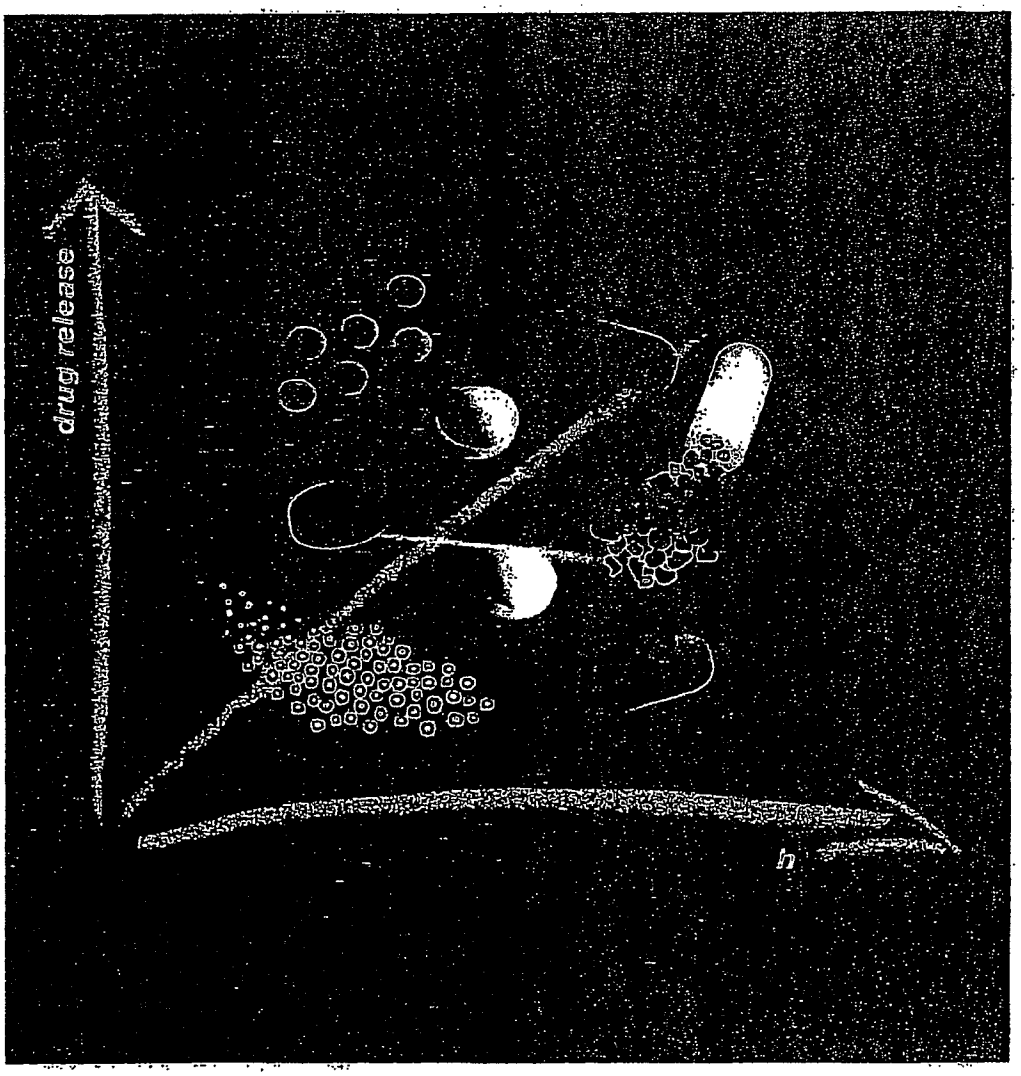
January 2004
Supersedes issue of June 1999

Register 2

Kollicoat® SR 30 D

® = Registered trademark of BASF Aktiengesellschaft.

Polyvinyl acetate dispersion for sustained-release pharmaceutical formulations



Contents

Microbiological status

Kollicoat® SR 30 D is not susceptible to microbial contamination. Microbiological testing is carried out in accordance with Ph. Eur., Category 3.

Unless otherwise stated, the methods of determination are taken from current European Pharmacopoeia.

2.3 Pharmacopoeia

A draft monograph Poly (Vinyl Acetate) Dispersion 30 per cent has been published in Pharmeuropa. Additionaly US-DMF was filed.

2.4 Marketing authorization

Polyvinyl acetate is described, with reference to oral administration, in Japanese Pharmaceutical Excipients (JPE) 1993. Polyvinyl acetate is used in a variety of medicinal products for oral administration in numerous countries including Germany, France and the USA.
Polyvinyl acetate is also used in the food industry, for example as a chewing gum base or for coating fruits and vegetables. It is listed, for example, in Germany in the Regulations for Marketing Authorization of Food Additives for Technological Purposes, in the USA in the Code of Federal Regulations, Section 172.615, in South Korea in the Public Code on Food Additives 1995 and in Japan in the Japanese Standard for Food Additives, March 1997.

3. Application and Processing

3.1 Application

Sustained-release coated formulations
Kollicoat® SR 30 D is used mainly for the manufacture of sustained-release dosage forms. Very effective control of drug release is achieved by coating pellets, granules and crystals.

Protective coats
Applied in small quantities or with hydrophilic additives, Kollicoat® SR 30 D provides good protection against odour or taste. It can also be used, for example as a subcoating, for isolating active ingredients to prevent interactions.

Sustained-release matrix formulations
Matrix tablets can be produced by granulating active ingredients, for example in the fluidized bed process, followed by compression.

3.2 Processing information

The dispersion is not particularly vulnerable to external influences. Nevertheless, the following factors could result in coagulate formation that precludes further use of the dispersion:

- addition of finely dispersed pigments
- high shear gradients in stirrers and mills
- addition of emulsifiers, stabilizers or wetting agents
- pH changes
- organic solvents
- foaming

The minimum film-forming temperature (MFT) of the pure dispersion is 18 °C. It can be lowered by adding plasticizers.

The dispersion can theoretically also be used without plasticizers, but these additives enhance film formation and the flexibility of the films.

The following are suitable as plasticizers or gloss enhancers:

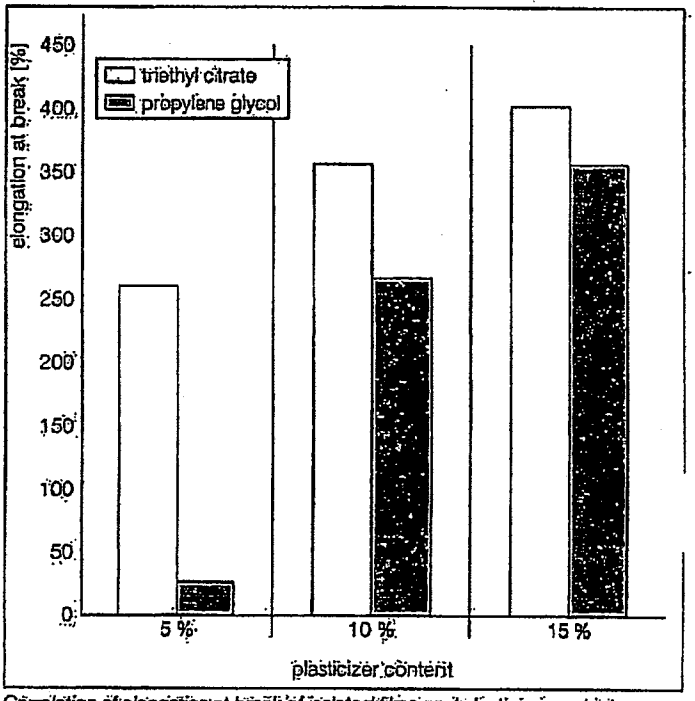
- 1,2-propylene glycol
- triethyl citrate
- polyethylene glycols and
- triacetin

The recommended plasticizer content is 0–10% with reference to the dried polymer substance

1,2-Propylene glycol offers advantages for processing the dispersion and for film properties.

Plasticizer supplement		MFT
2.5%	propylene glycol	18°C
5%	propylene glycol	16°C
10%	propylene glycol	14°C
15%	propylene glycol	12°C
2.5%	triethyl citrate	10°C
5%	triethyl citrate	8°C
10%	triethyl citrate	1°C
15%	triethyl citrate	< 0°C

Triethyl citrate lowers the MFT more than propylene glycol.
Kollicoat® SR 30 D films without plasticizer are relatively brittle in the dry state; when wet, however, they are very flexible (elongation at break > 100%).
A small plasticizer supplement also increases the flexibility of the polymer in the dry state. Elongation at break values of more than 250% can be achieved using 5% triethyl citrate or 10% propylene glycol. Crack formation in coats, due for example to pronounced swelling of the core, is thereby prevented.



Correlation of elongation at break of isolated films and plasticizer content

The permeability of the water-insoluble but swellable films can be varied by:

- the layer thickness of the coat
- the use of pore formers (Kollidon® VA 64, Kollidon® 30, HPMC, Avicel® PH 105). The required content depends on the desired release profile.

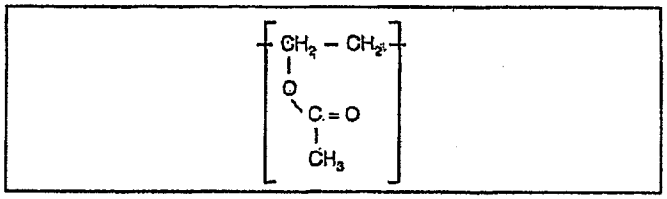
The layer thickness should not be less than 1.5 mg/cm² (= about 15 µm) since otherwise film defects and burst effects are to be expected.
Kollicoat® SR 30 D can be applied using either a top spray or bottom spray in the fluidized-bed coater.

1 Introduction

1.1 General

Kollicoat® SR 30 D is a polyvinyl acetate dispersion stabilized with povidone and sodium lauryl sulfate. The dispersion is suitable for the manufacture of pH-independent sustained-release formulations. The dispersion can also be used for taste masking.

1.2 Chemical structure



1.3 Trivial name

Poly (Vinyl Acetate) Dispersion 30 per cent

1.4 Commercial formulation

Kollicoat® SR 30 D is an aqueous dispersion with a solids content of 30%. The low viscosity product has a weak characteristic odour and a milky white or slightly yellowish appearance.

2 Specifications and properties

2.1 Description

The dispersion consists of about 27% polyvinyl acetate, 2.7% povidone and 0.3% sodium lauryl sulfate.

2.2 Physical and chemical properties

Identification:	Conforms
Film formation:	Conforms
Solubility:	Conforms
pH:	3.5–5.5
Relative density:	1.045–1.065
Viscosity	< 100 mPas
Coagulate content:	< 0.5%
Solids content:	28.5–31.5%
Sulfated ash:	< 0.5%
Heavy metals:	< 20 ppm
Monomers:	< 100 ppm
Microbiological status:	Conforms

Solubility

Kollicoat® SR 30 D is miscible with water in any ratio while retaining its milky-white appearance. Mixing the product with ethanol or isopropyl alcohol in a 1 : 5 ratio produces a slightly turbid and somewhat viscous solution; a solution in acetone is more turbid. On addition of organic solvents the polymer precipitates out but then dissolves when further solvent is added.
Kollicoat® SR 30 D is insoluble in dilute alkaline or acidic solutions. The dispersion retains a milky-white appearance.

Film formation

10 g of Kollicoat® SR 30 D are mixed with 0.3 g of propylene glycol. When poured onto a glass plate, a colourless or faintly yellowish film forms after the liquid has evaporated.

Viscosity

Viscosity is determined in accordance with DIN EN ISO 3219 at a shear gradient of 250 sec^{-1} and 23 °C.

Coagulate content

100 g of the substance is filtered through a 90 µm sieve. The residue is dried to constant weight at 105 °C in a drying oven.

Whether curing (thermal postcoating treatment) is necessary to achieve storage-stable drug release characteristics, should be determined on a casewise basis. The good film-coating properties generally mean that the film coat is insensitive to curing, in many cases, therefore, curing is unnecessary.
Kollicoat® SR 30 D has no charged or ionizable groups and consequently results in pH-independent film coats.

Using talc in the spray formulations reduces the sticking tendency thereby preventing agglomeration of small particles in the fluidized bed as well as adhesion effects.
Mixing the coated particles with 0.1–0.5% Aerosil® 200 prevents cohesion during storage even at elevated temperatures.

4. Formulation examples

4.1 Theophylline sustained-release pellets

Composition of spray suspension

The formulation is designed for 500 g pellets (diameter 0.8–1.3 mm)
Pellets: Spherofilin (Knoll AG)

	Parts by weight [g]	Composition [%]
Polymer suspension		
Kollicoat® SR 30 D	223.67	50.0
Propylene glycol	6.71	1.5
Water	149.86	33.5
Pigment suspension		
Kollidon® 30	2.24	0.5
Titanium dioxide	2.24	0.5
Sicovit® Red 30	2.24	0.5
Talc	15.66	3.5
Water	44.73	10.0
	447.35	100.0

Preparation of spray suspension

Polymer suspension:
Propylene glycol followed by Kollicoat® SR 30 D are added to the stated quantity of water with stirring.

Pigment suspension:
Kollidon® 30 is dissolved in the stated quantity of water. Sicovit® Red 30, titanium dioxide and talc are added with vigorous stirring and the mixture is homogenized with a corundum disk mill.

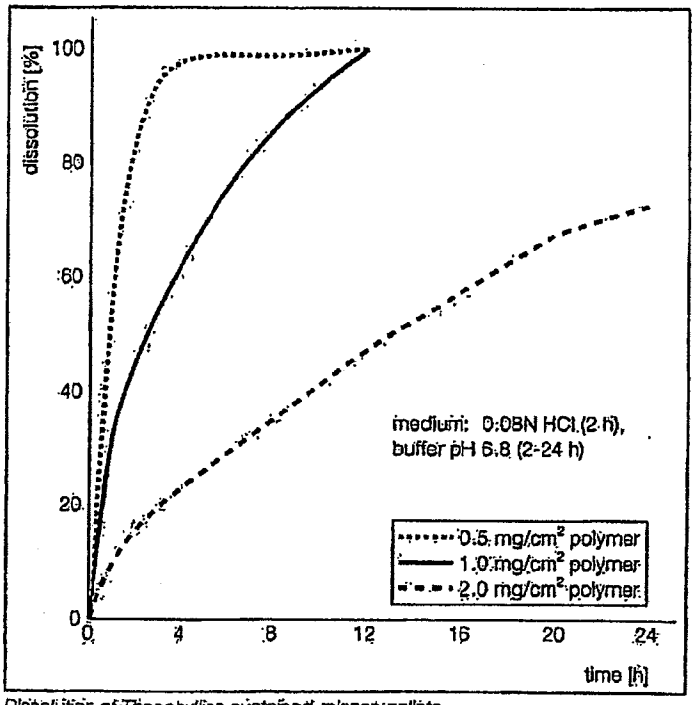
Spray suspension:
The pigment suspension is incorporated into the polymer suspension with stirring. The suspension must be stirred during the spray process to prevent settling.

Machine parameters

Machine	Aeromatic Strea-1 fluidized bed granulator
Batch size	500 g
Inlet air temperature	60°C
Outlet air temperature	37°C
Product temperature	38°C
Air flow	80 m³/h
Spraying pressure	1 bar
Spraying rate	11.5 g/min
Spraying time	39 min
Secondary drying	45°C/5 min
Coating level	2 mg film former/cm²

The spray suspension is sprayed continuously onto the fluidized, pre-heated pellets by the top spray method.

The coating level of 2 mg film former/cm² stated here was established for the pellets by surface area determination. Since the particle size distribution and surface structure influence the required polymer quantity, calculating the surface area is recommended as a means of estimating the required coating level in each specific case.



Dissolution of Theophylline-sustained-release pellets

4.2 Caffeine sustained-release pellets

Composition of pellets: 10% caffeine, 43.75% Avicel® PH 101, 43.75% lactose, 2.5% Kollidon® VA 64

Composition of spray suspension: The formulation is designed for 500 g pellets (diameter 0.7–1.4 mm)

	Parts by weight [g]	Composition [%]
Polymer suspension		
Kollicoat® SR 30 D	269.44	49.3
Propylene glycol	8.09	1.5
Water	188.61	34.5
Pigment suspension		
Kollidon® 30	2.7	0.5
Titanium dioxide	2.7	0.5
Sicovit® Red 30	2.7	0.5
Talc	18.87	3.4
Water	53.89	9.8
	547.99	100.0

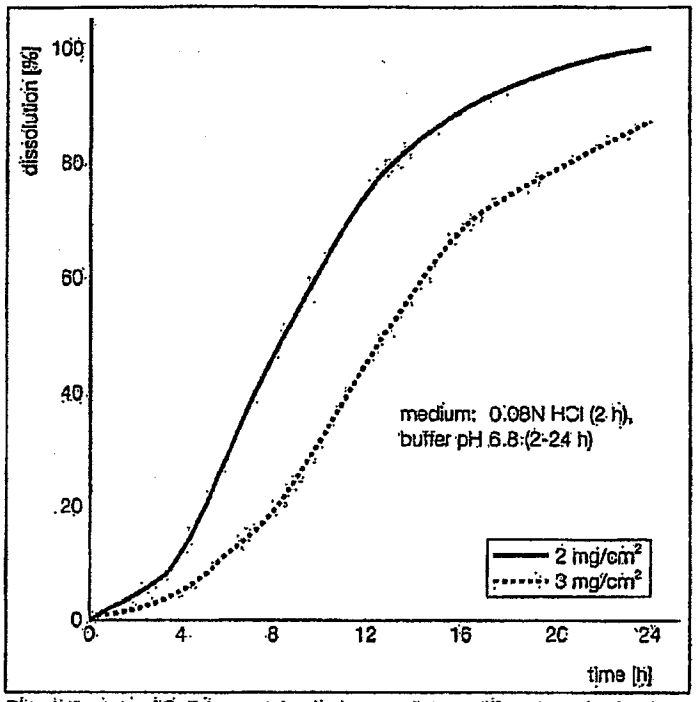
Preparation of spray suspension: *See Working Procedure 4.1*

Machine parameters:

Machine	Aeromatic Strea-1 fluidized bed granulator
Batch size	500 g
Inlet air temperature	60°C
Outlet air temperature	36°C
Product temperature	37°C
Air flow	80 m³/h
Spray pressure	1 bar
Spraying rate	12 g/min
Spraying time	45 min
Secondary drying	45°C/5 min
Coating level	3 mg film former/cm²

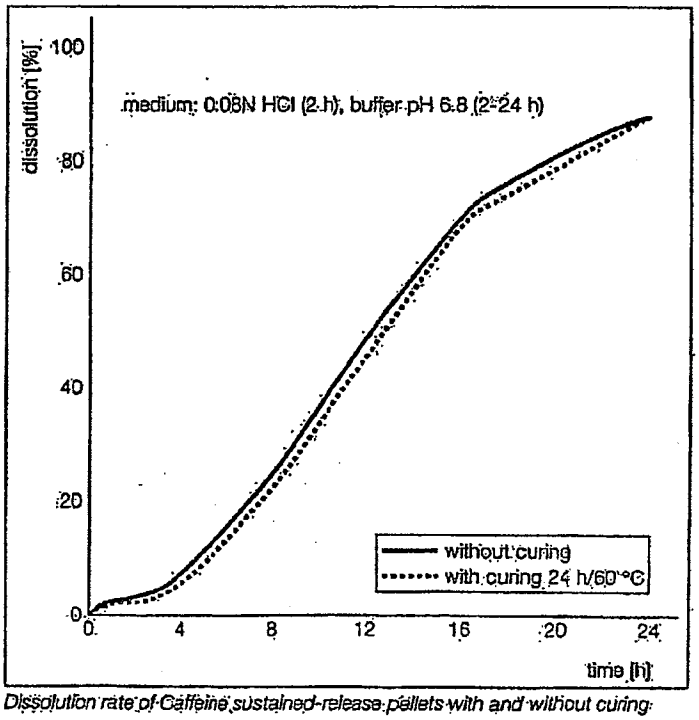
The spray suspension is sprayed continuously onto the fluidized, pre-heated pellets by the top spray method.

The coating level of 3 mg film former/cm² stated here was established for the pellets by surface area determination. Since the particle size distribution and surface structure influence the required polymer quantity, calculating the surface area is recommended as a means of estimating the required coating level in each specific case.

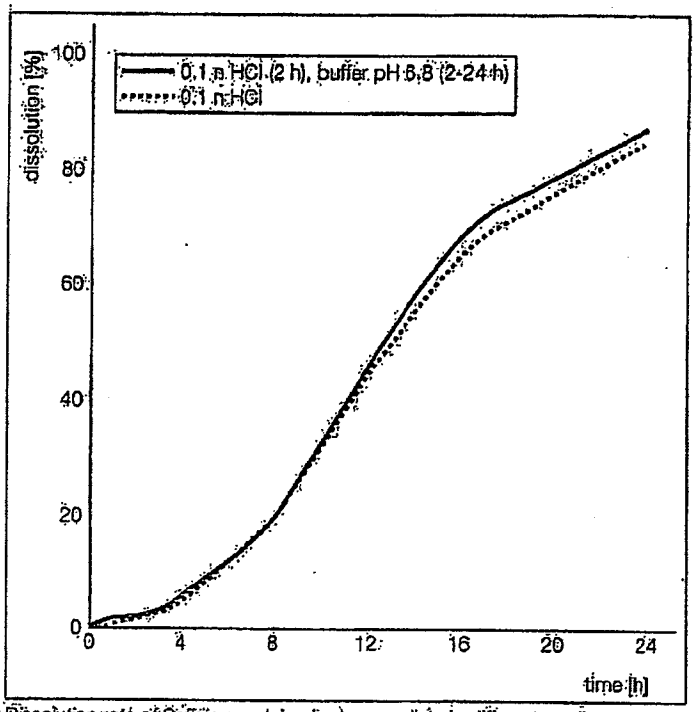


Dissolution rate of Caffeine sustained-release pellets at different coating levels

Curing (Thermal postcoating treatment) of the pellets is not necessary.



Dissolution rate of Caffeine sustained-release pellets with and without curing



Dissolution rate of Caffeine sustained release pellets in different media

The release of caffeine pellets is pH independent.

4.3 Propanol sustained release pellets

Composition of pellets: 20.0% propranolol, 51.66% Avicel® PH 101, 25.84% lactose, 2.5% Kollidon® VA 64

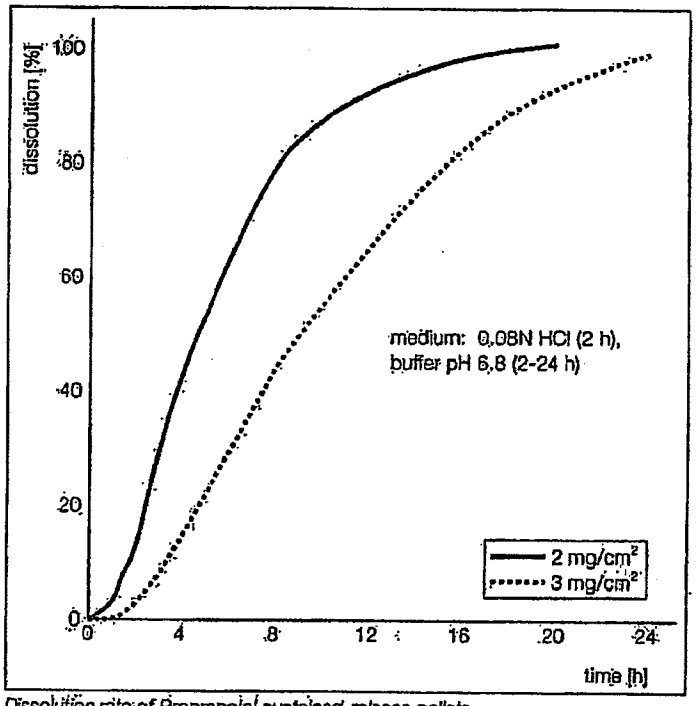
Composition of spray suspension *The formulation is designed for 500 g pellets (diameter 0.4–1.5 mm)*

	Parts by weight [g]	Composition [%]
Polymer suspension		
Kollicoat® SR 30 D	249.41	49.2
Propylene glycol	7.49	1.5
Water	174.59	34.5
Talc suspension		
Talc	29.94	5.9
Water	44.91	8.9
	506.34	100.0

Preparation of spray suspension *See Working Procedure 4.1.*

Machine parameters

Machine	Aeromatic Strea-1 fluidized bed granulator
Batch size	500 g
Inlet air temperature	60°C
Outlet air temperature	35°C
Product temperature	38°C
Air flow	80 m³/h
Spraying pressure	1 bar
Spraying rate	13 g/min
Spraying time	39 min
Secondary drying	45°C/5 min
Coating level	3 mg film former/cm²



Dissolution rate of Propranolol sustained-release pellets.

4.4 Taste-masked acetaminophen

Acetaminophen granules. (Knoll AG)

Smaller quantities have to be applied for taste masking since otherwise drug release characteristics would be excessively altered.

Crystalline acetaminophen is coated with 4% Kollicoat® SR 30 D.

The formulation is designed for 500 g powder.

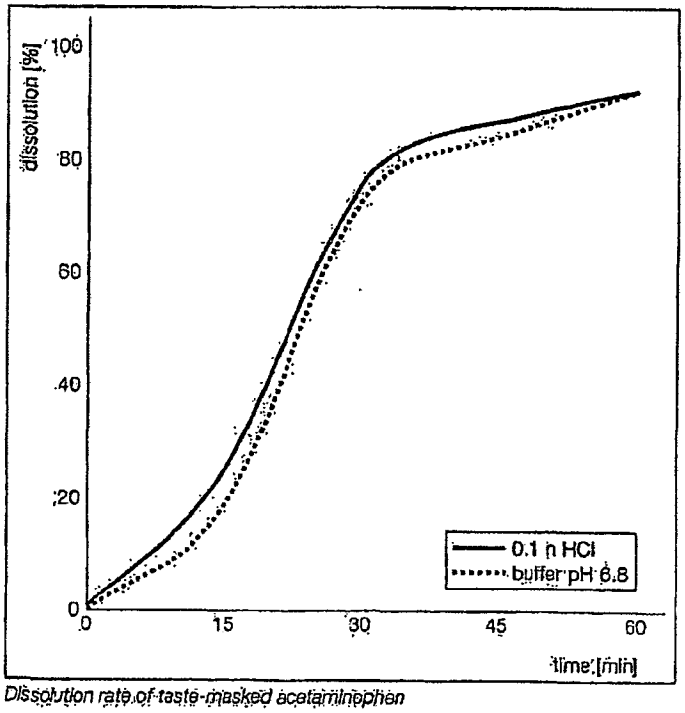
	Parts by weight [g]	Composition [%]
Polymer suspension:		
Kollicoat® SR 30 D	73.33	100.0

Machine parameters

Machine	Aeromatic Strea-1 fluidized bed granulator
Batch size	500 g
Inlet air temperature	60°C
Outlet air temperature	40°C
Product temperature	41°C
Air flow	80 m³/h
Spraying pressure	1 bar
Spraying rate	9 g/min
Spraying time	9 min
Secondary drying	45°C/5 min
Coating level	4%

Taste masking

No bitter taste



Dissolution rate of taste-masked acetaminophen

5. Storage	Protect from frost and store at 20°C
6. Stability	At least 18 months in the unopened original container. On exposure to heat and frost and if foaming occurs, aqueous dispersions may form coagulates that preclude further use of the product.
7. PBG No.	10201076
8. Packaging	25-l polyethylene container. The product can also be filled into larger containers.
Note	The data submitted in this publication are based on our current knowledge and experience. They do not constitute a guarantee in the legal sense of the term and, in view of the manifold factors that may affect processing and application, do not relieve processors from the responsibility of carrying out their own tests and experiments. Any relevant patent rights and existing legislation and regulations must be observed.

Technical Information

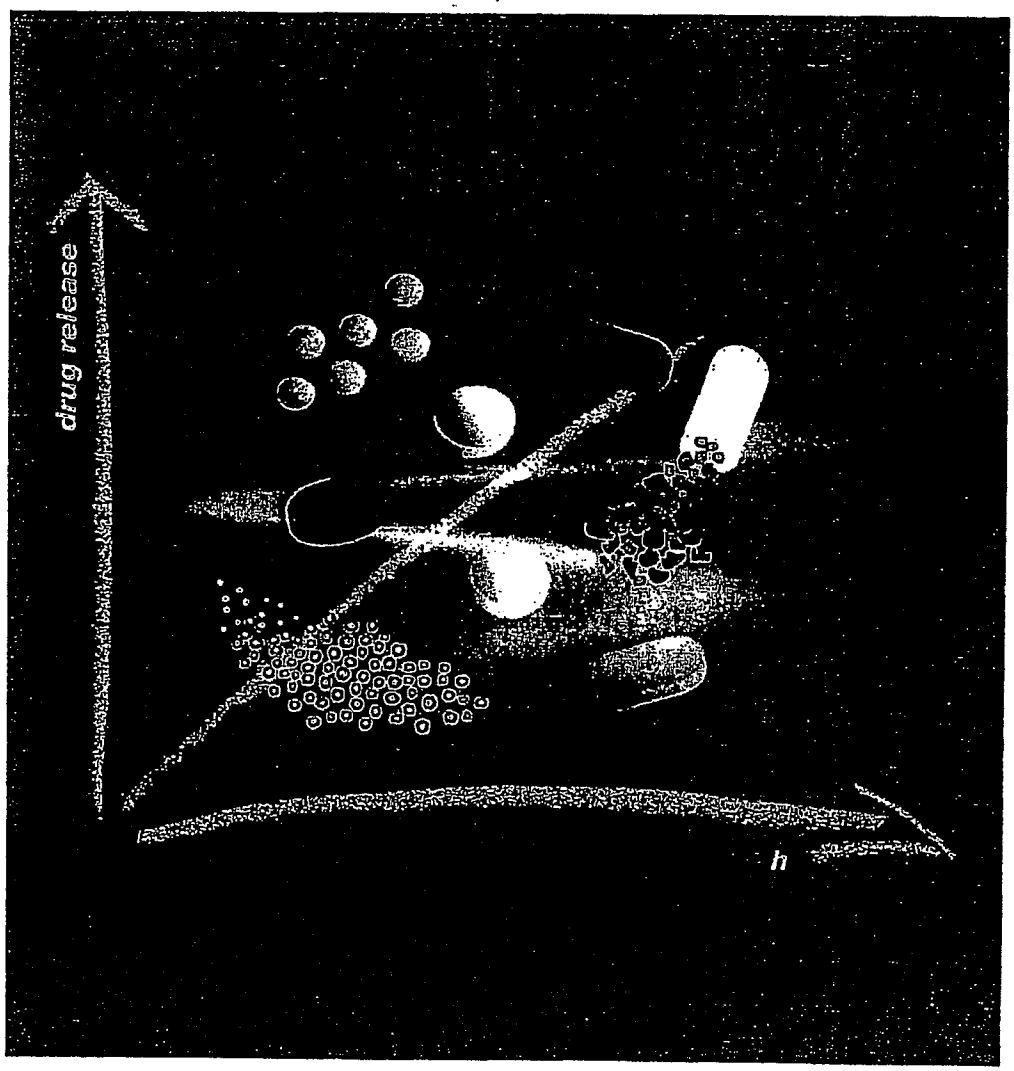
January 2004
Supersedes issue of June 1999

Register 2

Kollicoat® SR 30 D

® = Registered trademark of BASF Aktiengesellschaft

Polyvinyl acetate dispersion for sustained-release pharmaceutical formulations



Fine Chemicals

BASF

A-738

Contents:

Microbiological status	Kollicoat® SR 30 D is not susceptible to microbial contamination. Microbiological testing is carried out in accordance with Ph. Eur., Category 3.
	Unless otherwise stated, the methods of determination are taken from current European Pharmacopoeia.
2.3 Pharmacopoeia	A draft monograph Poly (Vinyl Acetate) Dispersion 30 per cent has been published in Pharmeuropa. Additionaly US-DMF was filed.
2.4 Marketing authorization	Polyvinyl acetate is described, with reference to oral administration, in Japanese Pharmaceutical Excipients (JPE) 1993. Polyvinyl acetate is used in a variety of medicinal products for oral administration in numerous countries including Germany, France and the USA. Polyvinyl acetate is also used in the food industry, for example as a chewing gum base or for coating fruits and vegetables. It is listed, for example, in Germany in the Regulations for Marketing Authorization of Food Additives for Technological Purposes, in the USA in the Code of Federal Regulations, Section 172.615, in South Korea in the Public Code on Food Additives 1995 and in Japan in the Japanese Standard for Food Additives, March 1997.

3. Application and Processing

3.1 Application

Sustained-release coated formulations
Kollicoat® SR 30 D is used mainly for the manufacture of sustained-release dosage forms. Very effective control of drug release is achieved by coating pellets, granules and crystals.

Protective coats
Applied in small quantities or with hydrophilic additives, Kollicoat® SR 30 D provides good protection against odour or taste. It can also be used, for example as a subcoating, for isolating active ingredients to prevent interactions.

Sustained-release matrix formulations
Matrix tablets can be produced by granulating active ingredients, for example in the fluidized bed process, followed by compression.

3.2 Processing information

The dispersion is not particularly vulnerable to external influences. Nevertheless, the following factors could result in coagulate formation that precludes further use of the dispersion:

- addition of finely dispersed pigments
- high shear gradients in stirrers and mills
- addition of emulsifiers, stabilizers or wetting agents
- pH changes
- organic solvents
- foaming

The minimum film-forming temperature (MFT) of the pure dispersion is 18 °C. It can be lowered by adding plasticizers.

The dispersion can theoretically also be used without plasticizers, but these additives enhance film formation and the flexibility of the films.

The following are suitable as plasticizers or gloss enhancers:

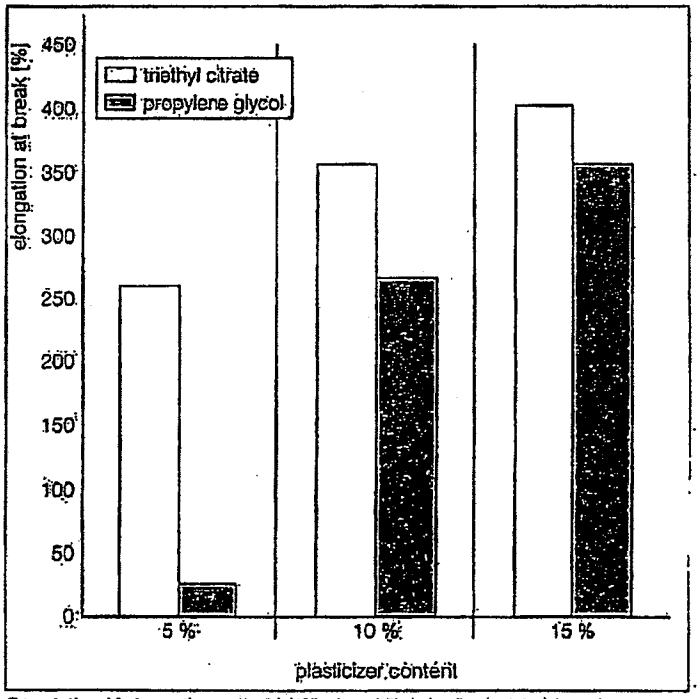
- 1,2-propylene glycol
- triethyl citrate
- polyethylene glycols and
- triacetin

The recommended plasticizer content is 0–10% with reference to the dried polymer substance.

1,2-Propylene glycol offers advantages for processing the dispersion and for film properties.

Plasticizer supplement		MFT
2.5%	propylene glycol	18°C
5%	propylene glycol	16°C
10%	propylene glycol	14°C
15%	propylene glycol	12°C
2.5%	triethyl citrate	10°C
5%	triethyl citrate	8°C
10%	triethyl citrate	1°C
15%	triethyl citrate	< 0°C

Triethyl citrate lowers the MFT more than propylene glycol.
Kollicoat® SR 30 D films without plasticizer are relatively brittle in the dry state; when wet, however, they are very flexible (elongation at break > 100%).
A small plasticizer supplement also increases the flexibility of the polymer in the dry state. Elongation at break values of more than 250% can be achieved using 5% triethyl citrate or 10% propylene glycol. Crack formation in coats, due for example to pronounced swelling of the core, is thereby prevented.



Correlation of elongation at break of isolated films and plasticizer content

The permeability of the water-insoluble but swellable films can be varied by:

- the layer thickness of the coat
- the use of pore formers (Kollidon® VA 64, Kollidon® 30, HPMC, Avicel® PH 105). The required content depends on the desired release profile.

The layer thickness should not be less than 1.5 mg/cm² (= about 15 µm) since otherwise film defects and burst effects are to be expected.
Kollicoat® SR 30 D can be applied using either a top spray or bottom spray in the fluidized-bed coater.

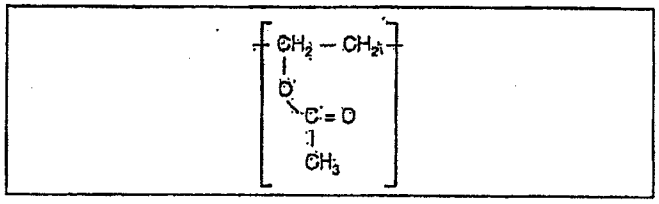
A-741

1 Introduction

1.1 General

Kollicoat® SR 30 D is a polyvinyl acetate dispersion stabilized with povidone and sodium lauryl sulfate. The dispersion is suitable for the manufacture of pH-independent sustained-release formulations. The dispersion can also be used for taste masking.

1.2 Chemical structure



1.3 Trivial name

Poly (Vinyl Acetate) Dispersion 30 per cent

1.4 Commercial formulation

Kollicoat® SR 30 D is an aqueous dispersion with a solids content of 30%. The low viscosity product has a weak characteristic odour and a milky white or slightly yellowish appearance.

2 Specifications and properties

2.1 Description

The dispersion consists of about 27% polyvinyl acetate, 2.7% povidone and 0.3% sodium lauryl sulfate.

2.2 Physical and chemical properties

Identification:	Conforms
Film formation:	Conforms
Solubility:	Conforms
pH:	3.5–5.5
Relative density:	1.045–1.065
Viscosity	< 100 mPas
Coagulate content:	< 0.5%
Solids content:	28.5–31.5%
Sulfated ash:	< 0.5%
Heavy metals:	< 20 ppm
Monomers:	< 100 ppm
Microbiological status:	Conforms

Solubility

Kollicoat® SR 30 D is miscible with water in any ratio while retaining its milky-white appearance. Mixing the product with ethanol or isopropyl alcohol in a 1 : 5 ratio produces a slightly turbid and somewhat viscous solution; a solution in acetone is more turbid. On addition of organic solvents the polymer precipitates out but then dissolves when further solvent is added.
Kollicoat® SR 30 D is insoluble in dilute alkaline or acidic solutions. The dispersion retains a milky-white appearance.

Film formation

10 g of Kollicoat® SR 30 D are mixed with 0.3 g of propylene glycol. When poured onto a glass plate, a colourless or faintly yellowish film forms after the liquid has evaporated.

Viscosity

Viscosity is determined in accordance with DIN EN ISO 3219 at a shear gradient of 250 sec^{-1} and 23 °C.

Coagulate content

100 g of the substance is filtered through a 90 µm sieve. The residue is dried to constant weight at 105 °C in a drying oven.

Whether curing (thermal postcoating treatment) is necessary to achieve storage-stable drug release characteristics, should be determined on a casewise basis. The good film-coating properties generally mean that the film coat is insensitive to curing. In many cases, therefore, curing is unnecessary.
Kollicoat® SR 30 D has no charged or ionizable groups and consequently results in pH-independent film coats.

Using talc in the spray formulations reduces the sticking tendency thereby preventing agglomeration of small particles in the fluidized bed as well as adhesion effects.
Mixing the coated particles with 0.1–0.5% Aerosil® 200 prevents cohesion during storage even at elevated temperatures.

4. Formulation examples

4.1 Theophylline sustained-release pellets

Composition of spray suspension

The formulation is designed for 500 g pellets (diameter 0.8–1.3 mm)
Pellets: Spherofillin (Knoll AG)

	Parts by weight [g]	Composition [%]
Polymer suspension		
Kollicoat® SR 30 D	223.67	50.0
Propylene glycol	6.71	1.5
Water	149.86	33.5
Pigment suspension		
Kollidon® 30	2.24	0.5
Titanium dioxide	2.24	0.5
Sicovit® Red 30	2.24	0.5
Talc	15.66	3.5
Water	44.73	10.0
	447.35	100.0

Preparation of spray suspension

Polymer suspension:
Propylene glycol followed by Kollicoat® SR 30 D are added to the stated quantity of water with stirring.

Pigment suspension:
Kollidon® 30 is dissolved in the stated quantity of water. Sicovit® Red 30, titanium dioxide and talc are added with vigorous stirring and the mixture is homogenized with a corundum disk mill.

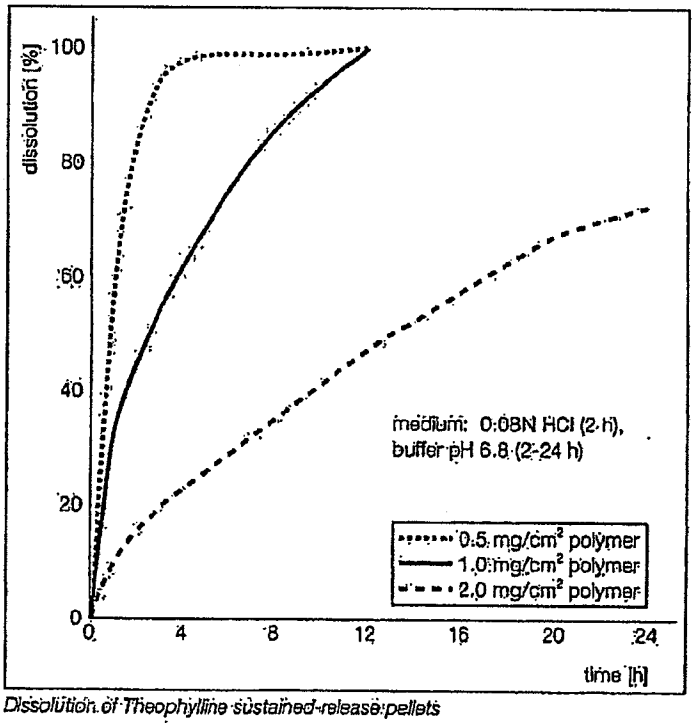
Spray suspension:
The pigment suspension is incorporated into the polymer suspension with stirring. The suspension must be stirred during the spray process to prevent settling.

Machine parameters

Machine	Aeromatic Strea-1 fluidized bed granulator
Batch size	500 g
Inlet air temperature	60°C
Outlet air temperature	37°C
Product temperature	38°C
Air flow	80 m³/h
Spraying pressure	1 bar
Spraying rate	11.5 g/min
Spraying time	39 min
Secondary drying	45°C/5 min
Coating level	2 mg film former/cm²

The spray suspension is sprayed continuously onto the fluidized, pre-heated pellets by the top spray method.

The coating level of 2 mg film former/cm² stated here was established for the pellets by surface area determination. Since the particle size distribution and surface structure influence the required polymer quantity, calculating the surface area is recommended as a means of estimating the required coating level in each specific case.



Dissolution of Theophylline sustained-release pellets

4.2 Caffeine sustained-release pellets

Composition of pellets: 10% caffeine, 43.75% Avicel® PH 101, 43.75% lactose, 2.5% Kollidon® VA 64

Composition of spray suspension: The formulation is designed for 500 g pellets (diameter 0.7–1.4 mm)

	Parts by weight [g]	Composition [%]
Polymer suspension		
Kollicoat® SR 30 D	269.44	49.3
Propylene glycol	8.09	1.5
Water	188.61	34.5
Pigment suspension		
Kollidon® 30	2.7	0.5
Titanium dioxide	2.7	0.5
Sicovit® Red 30	2.7	0.5
Talc	18.87	3.4
Water	53.89	9.8
	547.99	100.0

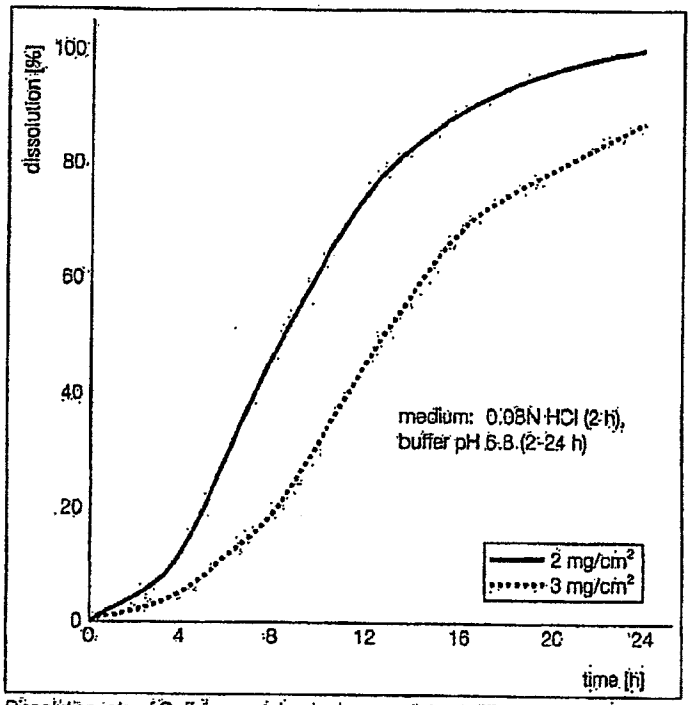
Preparation of spray suspension: *See Working Procedure 4.1*

Machine parameters:

Machine	Aeromatic Strea-1 fluidized bed granulator
Batch size	500 g
Inlet air temperature	60°C
Outlet air temperature	36°C
Product temperature	37°C
Air flow	80 m³/h
Spray pressure	1 bar
Spraying rate	12 g/min
Spraying time	45 min
Secondary drying	45°C/5 min
Coating level	3 mg film former/cm²

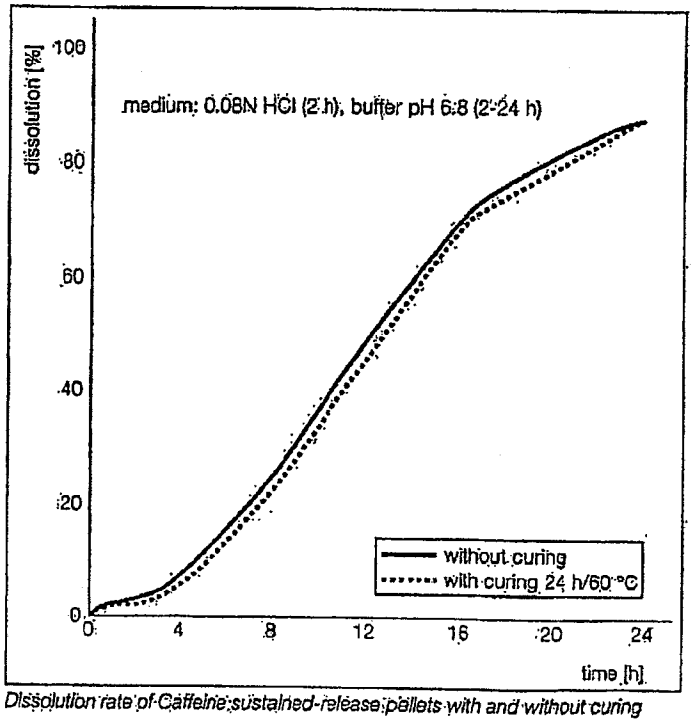
The spray suspension is sprayed continuously onto the fluidized, pre-heated pellets by the top spray method.

The coating level of 3 mg film former/cm² stated here was established for the pellets by surface area determination. Since the particle size distribution and surface structure influence the required polymer quantity, calculating the surface area is recommended as a means of estimating the required coating level in each specific case.

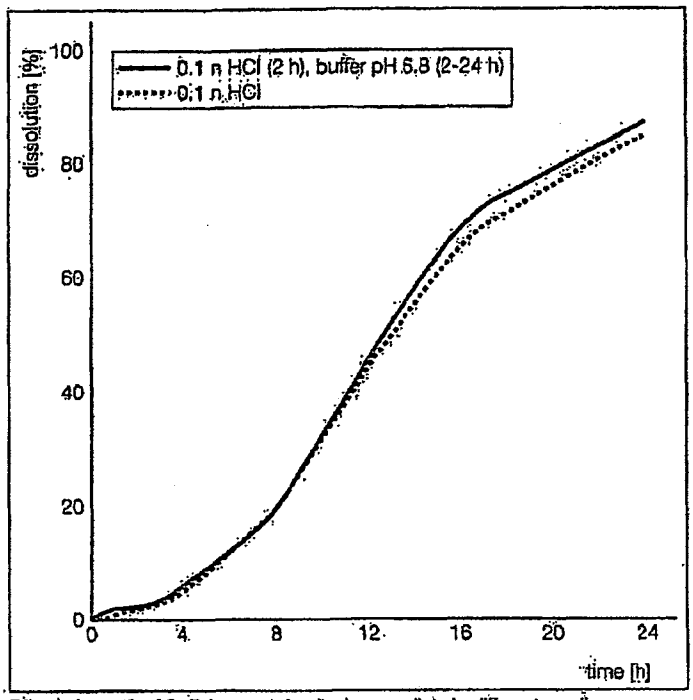


Dissolution rate of Caffeine sustained-release pellets at different coating levels

Curing (Thermal postcoating treatment) of the pellets is not necessary.



Dissolution rate of Caffeine sustained-release pellets with and without curing



Dissolution rate of Caffeine sustained-release pellets in different media

The release of caffeine pellets is pH independent.

4.3 Propanol sustained-release pellets

Composition of pellets: 20.0% propranolol, 51.66% Avicel® PH 101, 25.84% lactose, 2.5% Kollidon® VA 64

Composition of spray suspension

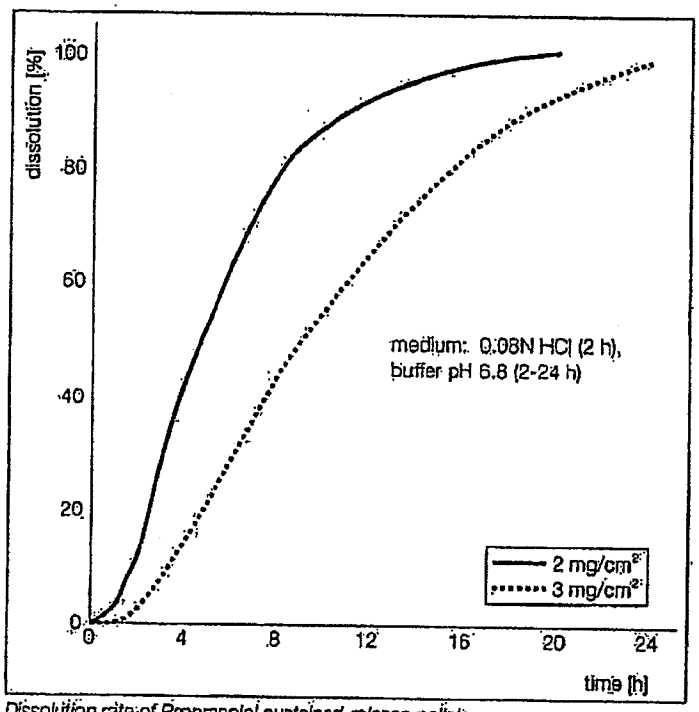
The formulation is designed for 500 g pellets (diameter 0.4–1.5 mm)

	Parts by weight [g]	Composition [%]
Polymer suspension		
Kollicoat® SR 30 D	249.41	49.2
Propylene glycol	7.49	1.5
Water	174.59	34.5
Talc suspension		
Talc	29.94	5.9
Water	44.91	8.9
	506.34	100.0

Preparation of spray suspension: *See Working Procedure 4.1.*

Machine parameters

Machine	Aeromatic Strea-1 fluidized bed granulator
Batch size	500 g
Inlet air temperature	60°C
Outlet air temperature	35°C
Product temperature	36°C
Air flow	80 m³/h
Spraying pressure	1 bar
Spraying rate	13 g/min
Spraying time	39 min
Secondary drying	45°C/5 min
Coating level	3 mg film former/cm²



Dissolution rate of Propranolol sustained-release pellets.

4.4 Taste-masked acetaminophen

Acetaminophen granules. (Knoll AG)

Smaller quantities have to be applied for taste masking since otherwise drug release characteristics would be excessively altered.

Crystalline acetaminophen is coated with 4% Kollicoat® SR 30 D.

The formulation is designed for 500 g powder.

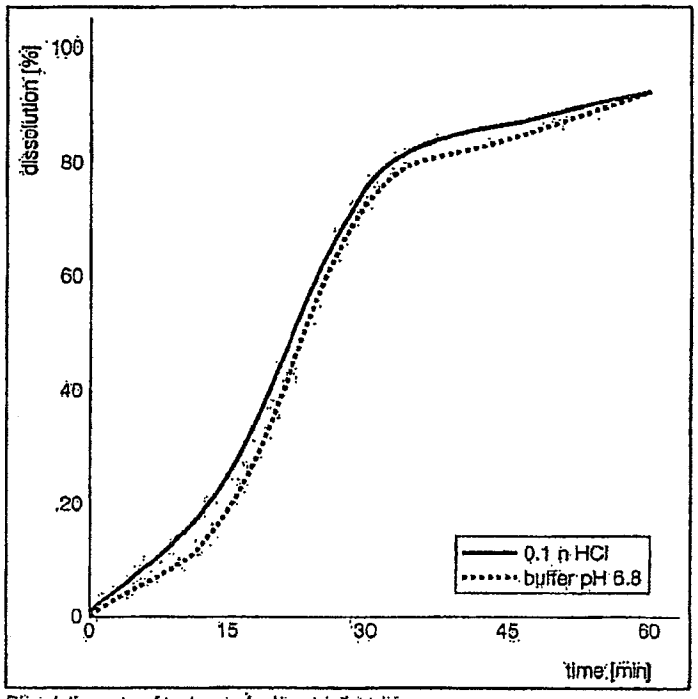
	Parts by weight [g]	Composition [%]
Polymer suspension		
Kollicoat® SR 30 D	73.33	100.0

Machine parameters

Machine	Aeromatic Strea-1 fluidized bed granulator
Batch size	500 g
Inlet air temperature	60°C
Outlet air temperature	40°C
Product temperature	41°C
Air flow	80 m³/h
Spraying pressure	1 bar
Spraying rate	9 g/min
Spraying time	9 min
Secondary drying	45°C/5 min
Coating level	4%

Taste masking

No bitter taste.



Dissolution rate of taste-masked acetaminophen

5. Storage	Protect from frost and store at 20°C
6. Stability	At least 18 months in the unopened original container. On exposure to heat and frost and if foaming occurs, aqueous dispersions may form coagulates that preclude further use of the product.
7. PBG No.	10201076
8. Packaging	25-l polyethylene container. The product can also be filled into larger containers.
Note	The data submitted in this publication are based on our current knowledge and experience. They do not constitute a guarantee in the legal sense of the term and, in view of the manifold factors that may affect processing and application, do not relieve processors from the responsibility of carrying out their own tests and experiments. Any relevant patent rights and existing legislation and regulations must be observed.

CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that on May 2, 2007, I electronically filed the foregoing with the Clerk of the Court using CM/ECF, which will send notification of such filing(s) to the following:

Richard L. Horwitz
POTTER ANDERSON & CORROON LLP

and that I caused copies to be served upon the following in the manner indicated:

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